Supreme Court, U.S.
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No. 85-1470

IN THE

Supreme Court of the United States

OCTOBER TERM, 1985

COMMUNITY NUTRITION INSTITUTE, *et al.*,
Petitioners,

v.

FRANK YOUNG, COMMISSIONER OF FOOD AND DRUGS
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE DISTRICT OF COLUMBIA CIRCUIT

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QUESTION PRESENTED

Whether the Food and Drug Administration is required, by the Food, Drug and Cosmetic Act, 21 USC 348(f)(1), to convene a public hearing into the safety and/or safe use of a food additive when requested to do so by any adversely affected person.

PARTIES TO THE PROCEEDING

The Petitioners are: the Community Nutrition Institute, a nonprofit nutrition research and education group specializing in providing information on federal feeding programs to churches and community groups; the Arizona Dietetic Association and Central Arizona District Dietetic Association, chapters of the American Dietetic Association, an organization of professional dieticians; Dr. Woodrow Monte, Ph.D., Professor of Food Science and Director of the Laboratory of Food Safety and Nutrition, Arizona State University.

The respondent is Dr. Frank Young, United States Commissioner of Food and Drugs.

TABLE OF CONTENTS

Page

OPINION BELOW 1

JURISDICTION 2

STATUTORY AND REGULATORY PROVISIONS INVOLVED 2

STATEMENT 2

REASONS FOR GRANTING PETITION 6

CONCLUSION 0

APPENDIX A 1a

APPENDIX B 23a

APPENDIX C 69a

APPENDIX D 70a

APPENDIX E 79a

APPENDIX F 81a

TABLE OF AUTHORITIES

Cases: Page

Dyestuffs and Chemicals, Inc. v Flemming,
271 F.2d 281 (8th Cir. 1959), *cert. den.* 362 U.S.
911 (1960) 7

Pactra Industries v CPSC,
555 F.2d 677 (9th Cir. 1977) 6

Statutes and Regulations:

United States Food, Drug and Cosmetic Act of 1938
as amended, 21 U.S.C. 321 §§ 348(f)(1) and (g)(1) 2

Miscellaneous:

49 Fed. Reg. 6672-6682 (1984) 2, 4

21 C.F.R. § 12.24..... 2, 3

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COMMUNITY NUTRITION INSTITUTE, *et al.*,
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FRANK YOUNG, COMMISSIONER OF FOOD AND DRUGS
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE DISTRICT OF COLUMBIA CIRCUIT

Petitioners seek a writ of certiorari to review the judgment of the United States Court of Appeals for the District of Columbia Circuit in this case.

OPINION BELOW

The opinion of the Court of Appeals (App., *infra*, 1a-22a) is reported at 773 F.2d 1356. The decision of the Food and Drug Administration (App., *infra*, p. 23a-68a) is reported at 49 Federal Register 6672-6682 (February 22, 1984).

JURISDICTION

The judgment of the court of appeals (App., *infra,* p. 81a) was entered on September 24, 1985. A petition for rehearing was denied on December 4, 1985 (App., *infra,* p. 69a), The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATUTORY AND REGULATORY PROVISIONS INVOLVED

Section 409 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 348, is reproduced at App., *infra,* p. 70a. Regulations of the Food and Drug Administration, 21 C.F.R. 12.24, are reproduced at App., *infra,* .

STATEMENT

This case concerns the denial by the United States Commissioner of Food and Drugs of petitioners' request for a public hearing on the safety of the unrestricted addition of aspartame (NutraSweet) to carbonated beverages. (49 FR 6672-6682, February 22, 1984, App. p. 23a-68a).

Petitioners requested a public hearing on August 8, 1983 following the Commissioner's July 8, 1983 approval of the addition of aspartame (NutraSweet) to carbonated beverages. Petitioners made the request for hearing in accordance with section 409 of the United States Food, Drug and Cosmetic Act (21 USC 348, App., *infra,* p. 70a-78a). The statute provides in pertinent part:

> (f)(1) Within thirty days after publication of an order made pursuant to subsection (c) or (d) of this section, any person adversely affected by such an order may file objections thereto with the Secretary, specifying with particularity the provisions of the order deemed objectionable,

> stating reasonable grounds therefor, and requesting a public hearing upon such objections. The Secretary *shall* after due notice, as promptly as possible hold such public hearing for the purpose of receiving evidence relevant and material to the issues raised by such objections. As soon as practicable after completion of the hearing, the Secretary shall by order act upon such objections and make such order public. [Emphasis added]
>
> . . .
>
> (g)(1) In a case of actual controversy as to the validity of any order issued under subsection (f), including any order thereunder with respect to amendment or repeal of a regulation issued under this section any person who will be adversely affected by such order may obtain judicial review by filing in the United States Court of Appeals . . . for the District of Columbia Circuit, within sixty days after the entry of such order, a petition that the order be set aside in whole or in part.

1. **Statutory and Regulatory Scheme.** The Food, Drug and Cosmetic Act prohibits the addition of an additive to food "if a fair evaluation of the data before the Secretary—(A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe" (21 USC 348(c)(3), **App. p. 72a-73a).**

Proponents of the use of a food additive are required to file evidence supporting their contention that the additive will be safe under the conditions of proposed use, including any proposed labeling provisions.

At the conclusion of its internal review process the agency publishes a proposed rule in the Federal Register and

adversely affected parties have thirty days to file objections and a request for a public hearing.

The Food and Drug Administration has adopted regulations designed to implement the public hearing provision of the statute (21 C.F.R. § 12.24(b), App., *infra*, p. 79a-80a).

2. **Proceedings Below.** Petitioners, three nutrition groups and a nutrition professor, objected to the unrestricted use of aspartame (NutraSweet) in carbonated beverages and sought a public hearing of their reasons. Petitioners contended that: (1) components of the additive reach the brains of individuals in amounts which raise serious questions of safety and which are higher than detected by the FDA; (2) the additive's reduced stability in liquids causes the creations of breakdown products that pose serious potential hazards to its consumers; (3) use of the additive in soft drinks increases consumption beyond acceptable levels posing potential safety problems; and (4) expanded consumption increases the risk, identified by external and internal FDA advisors,[1] that the additive might cause cancer.

Petitioners offered specific evidence on each issue and sub-issue raised. They contended that this evidence would cause a change in the facts supporting the regulation. They contended that this change of facts would cause, indeed require, the agency to find that the unrestricted use of aspartame in carbonated beverages had not been shown to be safe and therefore could not be allowed. Petitioners did

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[1]Cancer studies in the record led a three-scientist FDA Public Board of Inquiry to reject dry use of apartame in 1980. In 1981 a new Commissioner overruled the Board. In 1985 Sen. Howard Metzanbaum of Ohio sought, unsuccessfully, an *amicus curiae* role in the appeal and released memoranda supporting the Board's conclusion from the three FDA scientists asked to review it.

not base their case on proving, or offer to prove, that aspartame in carbonated beverages was "unsafe".

The agency denied the request for hearing on February 22, 1984 (49 Federal Register 6672-6682) (App., *infra.*, 23a). Petitioners appealed to the United States Court of Appeals for the District of Columbia Circuit which found against them. It is this decision which is the subject of this petition.

The appeals court commented on each disputed area. On brain damage it said Dr. Wurtman, cited by petitioners, failed "to *demonstrate* that these biochemical changes produced behavioral changes . . ." (App., *infra.*, p. 17a). The court said "the Commissioner concluded . . . that aspartame had not been *shown to cause* cancer . . ." (App., *infra.*, p. 20a. It said petitioners sought ". . . to *prove* the embryotoxic effects of DKP" (App., *infra.*, p21a). It summarized over 650 consumer complaints of injury due to aspartame saying the FDA found "no pattern of complaints that would indicate that aspartame was *unsafe.*" (App., *infra.*, p. 8a) [Emphasis added]

In each of these instances the court held that petitioners had failed to prove the addition of aspartame to carbonated beverages unsafe. The court relied on this failure to deny petitioners a public hearing. Petitioners contend the proper standard for granting a requested public hearing is the presenting of evidence that throws safety into doubt. The court concludes that in order for petitioner to obtain a public hearing its request must contain conclusive evidence persuasive to the FDA that the additive in question will cause harm to its consumers. However, under the law, if the FDA is persuaded of such a fact by such evidence its proper course of action is not to hold a public hearing but rather to restrict the use of the additive.

REASONS FOR GRANTING THE PETITION

As a matter of practice the food additive safety decisions made by the Food and Drug Administration are based almost exclusively, if not exclusively, on agency reviews of scientific data supplied by the petitioner for the use of the additive. Such petitioners almost invariably have a strong financial interest in the approval.

The process is a closed dialogue between the FDA and the petitioner for the additive. It is not until during the thirty days following the FDA's announcement of a proposed disposition of a food additive petition that the law provides for other interested parties (consumers, researchers, competitors, food processors who may buy the additive) the opportunity to present their knowledge, information and expertise in the food safety decision.

This opening to the broader community envisioned by the public hearing provisions of the law is an important part of the rule making process. In *Pactra Industries v. CPSC,* 555 F.2d 677 (9th Cir. 1977), cited in the agency denial of hearing, the court commented on the value of the statutory hearing, saying:

> These procedures permit affected parties to express in a direct and participatory manner their opposition and criticism of government action before it becomes final. The public, and the regulated industries, as well as the agency, develop a better understanding of the problems at hand by following these procedures, and the resulting regulation may be a more refined and precise statement of agency policy.

Denying a hearing when one should be granted distorts the societal impact of the regulatory process. Issues that could be sharpened, refined or disposed of remain to be

publicly troublesome. One hundred million people currently consume aspartame, scientists are locked in debate and thousands of complaints are received by government and private groups. But no hearing has been held to set the use of aspartame in carbonated beverages into a broadly understandable context shared by all the participants in the debate.

Until the aspartame ruling, the standard for conducting a public hearing was that set out in *Dyestuffs and Chemicals, Inc., v. Flemming,* 271 F.2d 281 (8th Cir. 1959) cert. den. 362 U.S. 911 (1960). That court wrote that "The objections must raise 'issues'. The issues must be material to the question involved; that is, the legality of the order attacked. They may not be frivolous or inconsequential." The standard for holding a public hearing should be "raising material issues", not "demonstrating lack of safety," which the appeals court has substituted in this case.

The appeals court decision, if allowed to stand, will shift the burden of proof of safety, and thus radically, and dangerously, alter the entire regulatory scheme for ensuring the safety of the United States food supply.

There is a further reason for reviewing the decision of the court of appeals in this case. If the standard enunciated by the court is followed by the agency, there will never be a basis for a public hearing, thus altering the statutory process for involving a broader segment of interested parties in the FDA's decision making.

Following the aspartame ruling it is necessary to persuade the FDA not only that the matters at hand are not frivolous or inconsequential but also that the evidence will prove the use of the additive unsafe. This standard not only undercuts the public hearing provisions, it moots them.

If a petitioner for public hearing meets this standard the FDA has grounds to restrict the use of the additive, and there is no need for a hearing.

But even more is at stake. When requested to hold a public hearing on the use of aspartame in dry foods in 1974, the agency agreed, including safety and *labeling* questions in the issues to be addressed. Because that hearing ended in disapproval of the use of aspartame in dry food (later overturned by the Commissioner), the labeling questions were never addressed in the hearing process.

As a result the FDA is on record at one point approving the need for a hearing on labeling questions and at another point opposing it. Since the hearing sought would address not only the safety of the substance but also the safety of the conditions of use of the substance the question of proper tolerances is also precluded from public deliberation.

By creating the situation where the holding of a public hearing is no longer a reasonable part of the food additive regulatory process the FDA and the appeals court have increased the likelihood that unsafe food additives will reach the market. Independent researchers, industrial competitors, potential food processing customers, and ultimate consumers are all precluded from the process.

This is an outcome not contained in the law and not conducive to the smooth running of the food market or to the health, safety and peace of mind of the American public.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

James S. Turner
Betsy E. Lehrfeld
Attorneys for Petitioners

March 1986

APPENDIX A

Notice: This opinion is subject to formal revision before publication in the Federal Reporter or U.S.App.D.C. Reports. Users are requested to notify the Clerk of any formal errors in order that corrections may be made before the bound volumes go to press.

United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 84-1153

COMMUNITY NUTRITION INSTITUTE, et al., PETITIONERS

v.

DR. MARK NOVITCH, ACTING COMMISSIONER,
FOOD AND DRUG ADMINISTRATION, RESPONDENT

G.D. SEARLE & CO., INTERVENOR

Petition for Review of an Order of the
Food and Drug Administration

No. 84-5253

COMMUNITY NUTRITION INSTITUTE, et al., APPELLANTS

v.

DR. MARK NOVITCH, ACTING COMMISSIONER,
FOOD AND DRUG ADMINISTRATION, APPELLEE

Bills of costs must be filed within 14 days after entry of judgment. The court looks with disfavor upon motions to file bills of costs out of time.

Appeal from the United States District Court
for the District of Columbia

(D.C. Civil Action No. 83-03846)

Argued January 25, 1985

Decided September 24, 1985

James S. Turner for petitioners/appellants.

David A. Levitt, Attorney, Department of Justice, with whom *J. Patrick Glynn*, Director, Office of Consumer Litigation, Department of Justice, and *Thomas Scarlett*, Chief Counsel, Food and Drug Administration, were on the brief, for respondent/appellee.

James R. Phelps and *Robert A. Dormer* were on the brief for intervenor G.D. Searle & Co.

Before: MIKVA, EDWARDS and STARR, *Circuit Judges*.

Opinion for the Court filed by *Circuit Judge* MIKVA.

MIKVA, *Circuit Judge*: These consolidated cases arose out of the Food and Drug Administration's ("FDA" or the "agency") approval, without a public hearing, of the food additive aspartame for use in liquids. Aspartame is an artificial sweetener more commonly known as NutraSweet, when used as a food additive, or as Equal, when used as a tabletop sweetener.

The underlying issue here is the FDA's action in approving the use of aspartame in liquids. Case No. 84-5253 is an appeal from the District Court's dismissal of a claim seeking to compel the FDA to conduct a hearing on aspartame, as well as a request to stay the approval pending the hearing, for lack of jurisdiction. In case No. 84-1153, we review the FDA's regulation approving the use of aspartame in liquids. For the reasons discussed

below, we affirm the decisions of both the District Court and the FDA.

I. BACKGROUND

Aspartame, a combination of two amino acids, phenylalanine and asparitic acid, was discovered and formulated by G.D. Searle & Co. ("Searle"), intervenor in this case, in the early 1970's. Because aspartame is approximately 180 times as sweet as sugar, it is an effective sugar substitute for those who wish to reduce their caloric intake or who must limit their consumption of sugar. Since the FDA issued its approval, aspartame is used in nearly all major brands of diet soft drinks, either in a blend with saccharin or as the sole sweetener ("wet use"). Aspartame is also used as a sweetener in a variety of non-carbonated beverage mixes and foods ("dry use"). We note that the dry use of aspartame, previously approved by the FDA, *see* 39 Fed. Reg. 27317 (July 26, 1974), is not on appeal here. While the proceedings surrounding the approval for dry use are helpful to our analysis of the instant appeal, we review here only the actions of the FDA and the District Court concerning the wet use of aspartame.

A. *Approval of Dry Use*

In March 1973, Searle filed a petition with the FDA for the approval of aspartame for use in certain dry foods such as powdered beverages, desserts and dessert toppings, and chewing gum as well as for use as a tabletop sweetener ("dry use"). 38 Fed. Reg. 5921 (Mar. 5, 1973). In July 1974, aspartame was approved for the requested dry uses, provided that two warning notices appear on products containing aspartame. 39 Fed. Reg. 27317 (July 26, 1974). The first warning is: "Phenylketonurics: Contains Phenylanine6." 21 C.F.R. § 172.804 (e) (2). This warning is necessary because a high plasma level of phenylalanine is associated with mental retardation in a small number of individuals with a genetic dis-

order that results in a lessened ability to metabolize phenylalanine. The second required statement cautions that aspartame for table use is not to be used in cooking or baking. 21 C.F.R. § 172.804(e)(3).

Two parties lodged objections to aspartame's dry use with the FDA. Dr. John Olney ("Olney") contended that the aspartic acid moiety of aspartame could cause brain lesions and neuroendocrine disorders in animals; therefore, according to Olney, aspartame posed a risk to human infants and children. 46 Fed. Reg. at 38285. James F. Turner, Esq. ("Turner"), who is counsel for petitioners in the instant cases, contended that phenylalanine moiety might lead to mental retardation. *Id.* Neither Olney nor Turner (collectively, the "objectors") are parties to the instant proceeding. The FDA granted the objectors' request for a hearing. Subsequently, the objectors and the FDA agreed to substitute a three member Public Board of Inquiry (the "Board") for the traditional hearing conducted by an Administrative Law Judge, as permitted by FDA regulations. *See* 21 C.F.R. Part 13. The Board was chosen by the FDA from a list of nominees submitted by the objectors. 46 Fed. Reg. 38286.

Before the hearing was convened, the FDA received reports that raised serious questions about the safety of aspartame and the methods by which it had been tested. In 1974, Searle submitted to the FDA a report of a study in which rats fed a principal degradation product of aspartame, called diketopiperazine ("DKP"), developed uterine polyps. Four teams of pathologists, including an FDA team, investigated the results to determine if the polyps revealed a safety hazard in connection with the consumption of aspartame. In addition, an FDA inspector filed reports that were critical of Searle lab practices, raising doubts as to the authenticity of Searle's reported data. An investigative task force appointed by the FDA found extensive problems with the quality and

reliability of Searle's research practices and test results relating to aspartame as well as to seven other products. The task force reported that the Searle research practices were so severely flawed that the test results were unreliable. As a result, in December 1975, the FDA stayed its approval of aspartame for dry use, *see* 40 Fed. Reg. 56907 (Dec. 5, 1975), and delayed convening the Board until Searle's aspartame safety studies could be audited.

Following the stay, fifteen of the Searle studies were selected for an audit as to authenticity, *i.e.*, that the tests and their results were neither faked nor misrepresented. The audit did not address the planning or execution of the studies or the correctness and meaning of the conclusions to be drawn from the studies. Twelve studies were audited by Universities Associated for Research and Education in Pathology (UAREP), a non-profit consortium of university pathologists. 46 Fed. Reg. at 38286. UAREP's inquiry was limited to "the question of whether the experiments were carried out according to protocol plans and the accuracy and reliability with which the experiments were performed and reported to FDA." *Id.* at 38302. The FDA reviewed the remaining three studies and found them to be authentic. In addition, the FDA examined UAREP's report and found that the test results described were authentic.

The Board was convened in January 1980. During three days of public hearings, the Board considered the following questions:

> 1. [W]hether the ingestion of aspartame, either alone or together with glutamate, poses a risk of contributing to mental retardation, brain damage, or undesirable effects on neuroendocrine regulatory systems[.]
>
> 2. [W]hether the ingestion of aspartame may induce brain neoplasms (tumors) in the rat[.]

3. Based on answers to the above questions,

(a) Should aspartame be allowed for use in foods, or, instead should approval of aspartame be withdrawn?

(b) If aspartame is allowed for use in foods, *i.e.*, if its approval is not withdrawn, what conditions of use and labeling and label statements should be required, if any?

44 Fed. Reg. at 31717. At the close of the hearings, the Board recommended that approval of aspartame be withdrawn until further study to establish whether or not a relationship existed between the ingestion of aspartame and brain tumors. As a result of this recommendation, the Board did not respond to the labeling question. The Board did agree with the FDA's determination that aspartame posed no risk of causing brain damage or endocrine dysfunction in people who used it. 46 Fed. Reg. 38288-89.

All parties to the Board's proceedings filed exceptions to its decision pursuant to 21 C.F.R. § 12.125. On July 24, 1981, the FDA issued a final decision, concurring with the Board's finding that aspartame would cause no brain damage or endocrine dysfunction, but overruling the Board's conclusion regarding brain tumors. Consequently, the FDA's decision reinstated approval of aspartame for dry use. 46 Fed. Reg. 38285. None of the parties to the proceeding appealed the FDA's decision to the Court of Appeals.

B. *Approval for Wet Use*

In October 1982, Searle filed a petition to amend the aspartame food additive regulation to include the wet use of aspartame. 47 Fed. Reg. 46140. The petition referenced, *inter alia*, the scientific data contained in the petition for approval of dry use. 48 Fed. Reg. at 31378. In July 1984, the FDA issued a final rule permitting

aspartame to be used in carbonated beverages and carbonated beverage syrup bases. *Id.* at 31376 (July 8, 1983) (amending 21 C.F.R. § 172.804 by adding § 172.804(c)(6)).

On August 8, 1983, the Community Nutrition Institute ("CNI"), Woodrow C. Monte, Ph.D. ("Monte") and Turner filed objections to the rule, and requested both a stay and a public hearing. The FDA denied the request for the stay. 48 Fed. Reg. 52899 (Nov. 16, 1983). On December 9, 1983, the Arizona Dietetic Association ("Arizona") and the Central Arizona District Dietetic Association ("Central") filed a Joinder of Petition, indicating they too objected to the rule. (We refer, hereafter, to these five individuals or organizations as "Appellants.") Also on December 9, Monte filed a supplement to his objections. On February 17, 1984, the FDA denied their objections and requests for a hearing on the ground that the objections failed to raise any genuine or substantial issue of fact. 49 Fed. Reg. 6672 (Feb. 17, 1984). On April 17, 1984, four of the objectors filed a petition for review of the FDA's denial of the hearing and interim stay. We review the actions of the FDA in Section III below.

C. *District Court Proceedings*

On December 23, 1983, while the request for a hearing was still pending before the FDA, the appellants also filed suit in District Court seeking an order requiring the FDA to hold a hearing and to stay the regulation until the hearing was completed. Thereafter, on January 24, 1984, the appellants filed a motion to stay the effective date of the approval of aspartame for both wet and dry use. The basis for the motion was a series of consumer complaints regarding adverse health effects caused by aspartame as well as new evidence from medical researchers calling into question the safety of aspartame. After a hearing, the District Court denied the

motion, finding that appellants' evidence was "anecdotal, unsubstantiated by direct scientific evidence and contains much that is hearsay." *Order*, Jan. 27, 1984.

On February 15, 1984, the appellants again filed a motion for a temporary restraining order supported by additional consumer complaints, affidavits describing issues that had been raised and considered by the Board in the dry use proceeding, and three letters from medical researchers commenting on various aspects of aspartame. In response to this second motion for a stay, the FDA filed a motion to dismiss, asserting that the district court lacked jurisdiction since judicial review of agency action or inaction was appropriate only in the Court of Appeals. The FDA also filed an Opposition accompanied by supporting affidavits, explaining that the FDA had reviewed the data provided by the appellants, but had found no pattern of complaints that would indicate that aspartame was unsafe.

Two days later, on February 17, 1984, the FDA denied the objectors' request for a hearing. Thereafter, on March 22, 1984, the District Court denied the second motion for a temporary restraining order and granted FDA's motion to dismiss the complaint on the ground that jurisdiction was lacking. The District Court concluded that since the "FDA [had] entered a final ruling on plaintiffs' request for an oral hearing and denied the hearings sought by the plaintiffs," only the Court of Appeals had jurisdiction. *See* Memorandum Order of Dismissal at 2.

II. The District Court Case: Jurisdiction

At issue in Case No. 84-5253 is whether the District Court erred in determining that it lacked jurisdiction once the FDA rejected Appellants' request for a hearing. In spite of the Food, Drug & Cosmetic Act's commitment to exclusive review in the Court of Appeals of final agency orders, appellants contend that policy dic-

tates permit the District Court to retain jurisdiction over a case even where the predicate for jurisdiction, here the lack of a final order, has evaporated. The policies underlying Appellants' argument are that first, a contrary holding would permit an agency to delay review by simply withholding final action until just before a district court holds a hearing; under this scenario, the FDA could lengthen the time for review of its action by the amount of time it takes to file in the District Court and obtain a hearing. Second, appellant argues that where there is no record to review, it is appropriate for a district court to have review in the first instance in order to develop the record.

We agree that the District Court did not have jurisdiction to review what had become a final order; by statute, such jurisdiction lies exclusively in the Court of Appeals. However, we find that the District Court erred in asserting jurisdiction over the case even before the FDA issued a final order; the FDA's ruling had no effect on the District Court's jurisdiction. Under the law of this circuit, the District Court *never* had jurisdiction over the agency's delay in ruling on the request for a hearing, neither before nor after the FDA denied the hearing request.

The question of where jurisdiction lies over interlocutory appeals from agency action (or inaction) has occasioned some anomalous results in the past. *Compare, e.g., Association of Nat'l Advertisers v. FTC*, 627 F.2d 1151, 1157 (D.C. Cir. 1979), *cert. denied*, 447 U.S. 921 (1980) (District Court had general federal question jurisdiction under 28 U.S.C. § 1331 over nonfrivolous constitutional claims of agency bias and prejudgment); *Public Citizen Health Research Group v. Commissioner, Food & Drug Administration*, 740 F.2d 21, 34-35 (D.C. Cir. 1984) (original jurisdiction of District Court not questioned, Court of Appeals remands to District Court for further evidence) *with Potomac Electric Power Co. v.*

ICC, 702 F.2d 1026, 1032-33 (D.C. Cir. 1983) (initially brought in Court of Appeals, jurisdiction upheld); *MCI Telecommunications Corp. v. FCC*, 627 F.2d 322 (D.C. Cir. 1980) (same). These inconsistent results signaled the need for close examination of the question of jurisdiction over interlocutory appeals. *See Telecommunications Research and Action Center v. FCC* (*"TRAC"*), 750 F.2d 70 (D.C. Cir. 1984).

In *TRAC*, this court fully resolved the issue, holding that

> Because the statutory obligation of a Court of Appeals to review on the merits may [pursuant to the All Writs Act] be defeated by an agency that fails to resolve disputes, a Circuit Court may resolve claims of unreasonable delay in order to protect its future jurisdiction.

750 F.2d at 76 (citations omitted). The jurisdiction to review agency inaction lies exclusively in this court. *Id.* at 77. We affirm the District Court's dismissal of the request for the hearing because that case could be heard only in this court.

Although jurisdiction over claims of nonfinal agency action or of agency inaction lies in this court, we exercise this jurisdiction reluctantly. Mandamus is an extraordinary remedy; we require similarly extraordinary circumstances to be present before we will interfere with an ongoing agency process. In assessing claims of agency delay, we are guided by a "rule of reason." 750 F.2d at 80. While there is no absolute definition of what is a reasonable time, we know that it may encompass "months, occasionally a year or two, but not several years or a decade." *See MCI Communications Corp. v. FCC*, 627 F.2d 322, 340 (D.C. Cir. 1980). In the past, unreasonable delays have been found where the agency had not acted in six years, *see Abbott Laboratories v. Harris*, 481 F. Supp. 74, 76-77 (N.D. Ill. 1979), and

after eight years, *see Potomac Electric Power Co. v. ICC*, 702 F.2d at 1033-35.

The delay complained of in the instant case was five months. Our precedents suggest that this is not an unreasonable delay. In addition, we note that the FDA's procedures, designed to be thorough and well-reasoned, do not permit quick decisions. A request for a hearing requires the agency to examine the record closely, because hearings are appropriate only where material objections to the FDA's actions exist. *See Pineapple Growers Ass'n v. FDA*, 673 F.2d 1083, 1085 (9th Cir. 1982); *Pactra Industries v. Consumer Product Safety Comm'n*, 555 F. 2d 677, 684 (9th Cir. 1977); *Dyestuff Chemicals, Inc. v. Flemming*, 271 F.2d 281, 286 (8th Cir. 1959), *cert. denied*, 362 U.S. 911 (1960). Requests for hearings must be accompanied by objections "specifying with particularity the provisions of the order deemed objectionable, stating reasonable grounds therefor." 21 U.S.C. § 348(f) (1982). The FDA has promulgated regulations that require the FDA to take a hard look at the objections. *See* 21 C.F.R. § 12.24(b)(1)-(3). While the FDA's denial of the hearing obviates our need to assess whether the instant case meets the mandamus standard, we could not say that a period of five months to accomplish the statutory mandate approached an "excessive" period.

In addition to a ruling on the request for a hearing, Appellants also sought a stay of the effective date of the rules approving both wet and dry use of aspartame until the hearing was held. Appellants argue that the District Court's jurisdiction over the stay continues even after the FDA issued its denial of the request for a hearing. As with the request for a hearing, we find that the District Court never had jurisdiction over the request for a stay. Stays of administrative action are properly sought in this court under a writ of mandamus. *See In re GTE Service Corp.*, 762 F.2d 1024, 1026 (D.C. Cir. 1985). The exclusive grant of jurisdiction to the

Court of Appeals means that mandamus to obtain a stay also is available only in this court. *See TRAC*, 750 F.2d at 78-79. Accordingly, we affirm the judgment of the District Court dismissing the request for a stay for want of jurisdiction.

III. THE FDA CASE

At issue in Case No. 84-1153 is whether the FDA acted within its discretion under the Food, Drug, and Cosmetic Act in denying Appellants a hearing on the possible dangers of aspartame in carbonated soft drinks and other "wet" uses. Under 21 U.S.C. § 348(g)(1), any person adversely affected by the FDA's denial of a hearing request may, within sixty days, petition for review of the denial in the Court of Appeals. The Commissioner denied Appellants' request for a hearing on February 22, 1984, 49 Fed. Reg. 6672, and they filed a petition for review of the FDA's denial of a hearing in this court on April 17, 1984. Because Appellants have filed a timely petition for review, their appeal is properly before us. Appellants contend that the Food, Drug & Cosmetic Act mandates a hearing when any interested party objects to the FDA's approval of a food additive as safe for a particular use. Appellants also argue that, even if an interested party is only entitled to a hearing upon a showing that a material issue of fact exists, they have met that burden.

We find that the FDA did not exceed its lawful discretion in denying a hearing to Appellants after the agency reviewed the record. The appellants raised no material objections to the safety of aspartame that would require the FDA to grant a hearing. Our review of the agency's action is limited to an evaluation of whether it has given adequate consideration to all relevant evidence on the record. We conclude that the FDA properly denied a hearing after finding that petitioners have raised no material issue regarding the safety of the wet use of aspartame.

At the outset it is essential to distinguish the proper subject matter of our review of the agency's action from the scope or intensity of our review. Our delineation of the proper subject matter is determined by the procedural history of the FDA's aspartame approval proceedings. Appellants raise a number of objections to the safety of the artificial sweetener. However, some of these objections overlap with or are identical to challenges to the safety of aspartame that the FDA has already considered and rejected when it approved aspartame for dry use. These issues may not be reopened. Since the only issue here is whether the FDA properly denied a hearing on the liquid uses of aspartame, only that evidence which bears on the dangers arising specifically from wet use is relevant to the FDA's determination that no material issues of fact existed. The agency's conclusions concerning the safety of the dry use of aspartame, except to the extent that new evidence suggests that the FDA may not rely on these prior findings in its deliberations on wet use, may not be raised again in this proceeding in the interests of administrative finality and judicial economy. *See Costle v. Pacific Legal Foundation*, 445 U.S. 198, 213, 217 (1980) (EPA permitted to condition an adjudicatory hearing, after its decision to extend a permit, on "identification of a disputed issue of fact by an interested party"); *Cooper Laboratories, Inc. v. Commissioner, Federal Food and Drug Administration*, 501 F.2d 772 (D.C. Cir. 1974). Thus we separate out those issues and that evidence which bear on the safety of wet use from the questions and data that were necessarily decided when the agency approved aspartame for dry use. The appellants may not now bring these dry issues before the FDA as reasons to require a hearing.

Having limited the issues which the FDA was required to consider before denying a hearing to Appellants, we next turn to the standard of review to apply in determining whether the FDA's denial of a hearing on that evi-

dence constituted an abuse of agency discretion. Our scope of review, the exactitude of the fit that we require between the agency's conclusions and the germane facts it investigated, is necessarily deferential. The judiciary is ill-equipped to conduct investigations and analyze facts of the type involved in this case. Because of the agency's expertise and broad discretion in ensuring the safety of food additives, we cannot substitute our judgment for the agency's. The Commission's finding that there were no material issues of fact can be overturned only if an examination of the record discloses that material issues of fact are apparent to any reasonable examiner. *Smith-Kline Corp. v. Food and Drug Administration*, 587 F.2d 1107, 1119 (D.C. Cir. 1978) (record must disclose genuine issue of fact to be resolved in order for court to order hearings); *Greater Boston Television Corp v. FCC*, 444 F.2d 841, 851 (D.C. Cir. 1970), *cert. denied*, 403 U.S. 923 (1971) (judicial review of agency's denial of hearing request need only "assure that the agency has given learned consideration to all the material facts and issues"). Mere differences in the weight or credence given to particular scientific studies, or in the numerical estimates of the average daily intake levels of aspartame, are insufficient. The court will not substitute its judgment on highly technical and factual matters for that of the agency charged with the supervision of the industry. *See Udall v. Tallman*, 380 U.S. 1 (1965).

A. *The Statutory Provision for a Hearing*

Under such limited scope of review and a delineation of the issues upon which the review must be focused, we conclude that Appellants have failed to demonstrate that the FDA abused its discretion by denying a hearing. The FDA's decision to approve a food additive is governed by Section 409 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 348. Under this statute, a new food additive is to be approved if a "fair evaluation" of the data indicates the safety of the ingredient. *Id.* at § 348(c)(3).

FDA has interpreted "safety" to mean "that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use." 21 C.F.R. § 170.3(i). Appellants argue that the Act mandates a nondiscretionary grant of a hearing by the FDA upon the objection of an interested party. That is not what the statute says. A hearing is only available if petitioners raise a material issue in their objections. The statute provides that any person adversely affected by the approval or rejection of a food additive petition may within thirty days of the order file objections and request a hearing. 21 U.S.C. § 348(f)(1). However, the statute requires that the objections specify with particularity the provisions of the order deemed objectionable and state reasonable grounds for the objections. The Secretary shall hold such hearing *for the purpose of receiving evidence relevant and material to the issues raised by such objections.* If the agency determines that no hearing is necessary, the regulation approving the food additive becomes final.

It is well established that the statutory grant of a public hearing is not absolute. A request for a hearing must contain evidence that raises a material issue of fact on which a meaningful hearing might be held. *Pineapple Growers Ass'n v. FDA*, 673 F.2d 1083, 1085 (9th Cir. 1982). In addition, the issue of fact raised by the objecting party must go to the legality of the agency's order. *Id.* at 1085, quoting *Dyestuffs and Chemicals v. Flemming*, 271 F.2d 281, 286 (8th Cir. 1959), *cert. denied*, 362 U.S. 911 (1960) ("Where the objections stated and issues raised thereby are, even if true, legally insufficient, their effect is a nullity and no objections have been stated.") The FDA's own regulations reflect this requirement that a challenge to an agency's factual conclusion must present a live controversy and affect the legality of the agency's determination to act in a certain way. *See Weinberger v. Hynson, Westcott & Dunning,*

Inc., 412 U.S. 609, 620-22 (1973). In 21 C.F.R. § 12.24 (b), the FDA requires that a person seeking to justify a hearing on objections to approval of a food additive must show 1) the existence of a genuine and substantial issue of fact to be resolved at a hearing; 2) that the factual issue can be resolved by available reliable evidence; 3) the objecting party's data and information, if proved, would be sufficient to resolve the factual issue in the way sought by the objecting party; and 4) resolution of the factual issue in that way would suffice to warrant the relief requested. If the objecting party fails to make these threshold showings, the FDA denies the hearing request.

B. *The FDA's Examination of the Evidence of the Dangers of Aspartame for Wet Use*

As pointed out above, Appellants may obtain a hearing on issues decided during the approval of aspartame for dry use only if they introduced new evidence suggesting that reliance on those issues in the context of wet use is erroneous. Appellants contend that they have introduced this new evidence on the questions of: 1) the relationship between the ingestion of aspartame and brain lesions, mental retardation, and mental instability; 2) the availability of new and more sophisticated tests for the formation of the toxic chemical nitrosamine as a result of aspartame ingestion; 3) the increase in average daily consumption of aspartame resulting from its use in carbonated beverages; 4) the carcinogenicity of aspartame; and 5) the labeling requirements for aspartame. Our review of each of these contentions leads us to conclude that Appellants have not introduced any new evidence suggesting that the FDA, in its approval of aspartame for wet use, abused its discretion in relying on tests and studies conducted previously in connection with the effects of consuming aspartame in dry uses.

1. *Brain Damage.* Appellants argue that there is a material issue of fact on whether the approval of as-

partame for carbonated beverage use would increase the level of phenylalanine in blood plasma, which would in turn cause changes in the production of the brain's neurotransmitters. Petitioners then speculate that these changes might lead to aberrations in behavior. In support of this argument, Appellants cite letters from Dr. Richard Wurtman to the director of the Bureau of Foods at the FDA. Two effects concerned Dr. Wurtman. First, his data indicated that large doses of aspartame given to humans and rats after they had been deprived of food increased the concentration of two amino acids, phenylalanine and tyrosine, which control production of two brain neurotransmitters, norephinephrine and dopamine. However, Dr. Wurtman did not demonstrate that these biochemical changes produced behavioral changes in humans or animals. In addition, another study, cited by the FDA in the preamble to the carbonated beverage approval, 48 Fed. Reg. 31379, found that high doses of aspartame did not significantly influence the amounts of either neurotransmitter in the brains of the subjects. Second, Dr. Wurtman was concerned that aspartame would interfere with the production of another neurotransmitter, serotonin, that normally occurred when sated rats were fed large amounts of carbohydrates. Dr. Wurtman asserted that aspartame's effect on neurochemical activity in the brain had previously been estimated without consideration of the effect of carbohydrates. Dr. Wurtman maintained that aspartame's effects could be "markedly amplified" when the sweetener was ingested with carbohydrates that consumers probably would consume at the same time as carbonated soft drinks. However, Dr. Wurtman failed to provide empirical support for his hypothesis that aspartame interferes with carbohydrates' usual effect of inducing serotonin production. The Commissioner evaluated this study, and concluded that the agency had fully evaluated all the issues about the safe use of aspartame in carbonated beverages.

Appellants also cite an assertion by Dr. Paul LeChance that the increased use of aspartame resulting from the addition to carbonated beverages may result in a narrowed "margin of safety between what could be labeled psychological levels of amino acids in a population known to consume high protein diets, and pharmacological levels with the possibility of exerting excitatory [sic] over time, and possible brain lesions. . . ." The FDA concluded that "an adequate margin of safety exists between the levels of phenylalanine [a component of aspartame] known to produce mental retardation and those resulting even from exaggerated exposure to aspartame in carbonated beverages." 49 Fed. Reg. 6674.

2. *Nitrosamines.* Nitrosamines, believed to be carcinogenic, are compounds that theoretically might result from the breakdown of aspartame and of diketopiperazine (DKP), a breakdown product of aspartame. The agency, however, basing its findings on Searle experiments which attempted to create nitrosamines under ideal laboratory conditions, concluded that "stable nitrosamines were extremely difficult to form," and that "any amounts that could be formed were extremely unstable under conditions that would occur in the gastrointestinal system." *Id.* at 6674, 6677. Appellants have argued that the FDA should reopen the search for carcinogenic nitrosamines, citing the emergence of new analytical techniques since 1974 that enabled investigators to detect nitrosamine in malt beverages. We conclude that the FDA acted well within its discretion in concluding, based upon its expert review of the record, that Appellants offered no evidence that the "formation of nitrosamines in malt beverages has any possible relevance to structurally dissimilar nitrosamine formation in soft drinks containing aspartame." *Id.* at 6677. Absent proof by Appellants that new scientific procedures were relevant to beverages containing aspartame, FDA could as a matter of policy decide against requiring additional testing without holding a hearing on the issue.

3. *Increased Consumption.* Appellants maintain that the FDA's previous estimates of daily aspartame consumption, which formed the basis for its conclusion that dry use of aspartame was safe, cannot form the basis for approval of aspartame in wet uses without a hearing. The premise of Appellants' argument is that wet use will increase the overall average consumption of aspartame. Our review of the record convinces us that the FDA gave proper consideration to the effect of liquid use on overall consumption in concluding that the public would not be exposed to danger. In its hearing on dry use of aspartame, the Public Board of Inquiry used the consumption estimate of 34 mg of aspartame/kilogram (mg/kg) of body weight as the 99th percentile of estimated daily consumption for all age groups. 46 Fed. Reg. 38289-90. This estimate means that only one percent of those who consume aspartame would consume more than 34 mg/kg a day, while the vast majority of consumers would have lower consumption levels. Significantly, this 34 mg/kg figure was based on the assumption that aspartame would be used in the foods sought for approval in the dry use petition, in a number of other foods, and as the *only sweetener* in all carbonated beverages. *Id.* at 38285, 38290. The FDA also projected that an average daily intake of 50 mg/kg of body weight would be safe. 49 Fed. Reg. 6672, 6677, 6679. Since the FDA observed that the "no effect" dose for aspartame (the highest level at which no toxic effects on experimental animals were observed) was between 2000 and 4000 mg/kg of body weight, the agency concluded that a 50 mg/kg intake body weight was safe. The safety factor, between forty-fold and eighty-fold, provides a conservative safety margin; it indicates that the average daily consumption could be multiplied by that factor without exceeding the "no effect dose" of aspartame. *Id.* at 6677-78. Appellants also allege that some patterns of consumption of carbonated beverages—for example, drinking several cans in rapid succession on a hot

day—would lead to higher concentrations of aspartame. The FDA acknowledged that some consumers may exceed 34 mg/kg of aspartame on some days, particularly consumers in hot weather or consumers, such as children, who have low body weight. 49 Fed. Reg. 6678. The agency, however, noted that studies conducted by Searle Laboratories, intervenors/respondents in this case, indicated that even levels of 200 mg/kg of body weight in a single dose did not produce acute toxicity. This concentration is the level that would result from a normal adult's consumption of 5.5 pounds of sugar or 13 quarts of orange soda containing aspartame in a single sitting. 48 Fed. Reg. 31380; 49 Fed. Reg. 6676. The FDA could properly exercise its discretion in deciding that "the pattern of aspartame ingestion over the day is not important as long as the total amount ingested per day does not exceed the 200 mg/kg level shown to be safe." 49 Fed. Reg. at 6678. We find no reason to disturb this conclusion.

4. *Carcinogenicity.* Appellants attempt to reopen the issue of the carcinogenicity of aspartame and its breakdown products. Although the Commissioner concluded, based on the dry use proceeding, that aspartame had not been shown to cause cancer, *Id.* at 6672, 6679-80, Appellants challenge this conclusion by attacking one of the studies that provided support for the Commissioner's conclusions. No party contested the agency's reliance on the study during the dry use proceeding. Nor do Appellants point to specific deficiencies in the study which have come to light since the time for appeal expired. We find that Appellants have failed to create a material issue on the carcinogenicity of aspartame that the agency overlooked in its decision to deny a hearing in this case.

5. *Labeling Requirements.* Appellants assert that the conditions of use and required labeling statements for aspartame in liquid use are new issues that the Public Board of Inquiry did not address. The Board and the FDA, however, have considered the issue of appropriate

warnings. The Board required a caution to patients with phenylketonuria that aspartame contained phenylalanine. In addition, the Commissioner's dry use approval in 1981 required a statement on the label that aspartame, when packaged as a tabletop sweetener, should not be used in cooking or baking. 21 C.F.R. § 172.804(e)(3). Appellants' current objections do not present any new evidence or suggest any material issue of fact about the necessity of additional warning or labeling requirements.

Appellants also raise a number of issues which they maintain are unique to wet use and therefore were properly excluded from the dry use studies. Specifically, Appellants claim that wet use of aspartame 1) has a toxic effect on human embryos; and 2) decomposes at higher temperatures in a more dangerous way than aspartame carried in dry mediums. We find no evidence on either of these points that would require the FDA to hold a hearing.

1. *Danger to Fetuses.* Diketopiperazine (DKP) is the principal degradation product of aspartame. Seeking to prove the embryotoxic effects of DKP, Appellants advance a letter from Dr. Jean Lederer, reporting on his administration of DKP to rats. The FDA weighed this evidence, and concluded that aspartame and its breakdown products did not produce fetal damage. 49 Fed. Reg. 6682. Dr. Lederer could not associate fetal damage with aspartame, 48 Fed. Reg. 31380. In its approval of July 8, 1983, the FDA concluded from Dr. Lederer's report, "Aspartame and its Effect on Gestation in the Rat," that animals fed at the highest level of DKP in the diet showed no embryotoxic effects.

2. *Decomposition.* Appellants argue that the use of aspartame in carbonated beverages is qualitatively different from its use in dry foods. They base this argument on the claim that carbonated liquid is peculiarly susceptible to changes of temperature and quality of the medium that lead to the breakdown of a large amount of

the aspartame present in the liquid. In addition, Dr. LeChance asserted that the presence of carbonated beverages in distribution channels in "subtropical temperature conditions" during the summer months would lead to "deterioration of DKP and release of the free amino acids . . . ." It was within the FDA's discretion to conclude, based on its expert review of the evidence, that no safety issues respecting aspartame's instability at high temperatures warranted a hearing. 48 Fed. Reg. 31376-77, 31381.

We conclude that Appellants have failed to raise any material issues of fact requiring the FDA to grant a hearing. Therefore, we affirm the FDA's decision in Case No. 84-1153 to deny Appellants a hearing on the wet use of aspartame. In Case No. 84-5253, we affirm the District Court's dismissal for lack of jurisdiction of Appellants' request for a stay of approval pending the hearing.

It is so ordered.

APPENDIX B

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
21 CFR PART 172
[DOCKET NOS. 75F-0355 AND 82F-0305]
FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION: ASPARTAME

AGENCY: Food and Drug Administration

ACTION: Denial of requests for hearing; final rule-related.

SUMMARY: The Food and Drug Administration (FDA) is denying the requests for a hearing on certain safety issues related to the amendment to the food additive regulation concerning aspartame that provides for the safe use of the substance in carbonated beverages and carbonated beverage syrup bases. After reviewing the objections to the amendment and the requests for a hearing, FDA has concluded that the objections do not raise issues of material fact that justify granting a hearing on a food additive regulation.

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SUPPLEMENTARY INFORMATION:

I. INTRODUCTION

Aspartame (*N-L-a*-aspartyl-*L*-phenylalanine 1-methyl ester) is the nutritive methyl ester of a dipeptide formed from phenylalanine and aspartic acid. G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077, originally petitioned in 1973 for approval of its use as a sweetener and flavor enhancer in dry foods. FDA approved the petition in a final regulation published in the FEDERAL REGISTER of July 26, 1974 (39 FR 27317), and codified at 21 CFR 172.804.

FDA received formal objections to this regulation and requests for a hearing to investigate certain alleged toxic effects of aspartame. FDA granted the request for a hearing and etablished a Public Board of Inquiry (the Board), nominated from scientists outside the agency, to hear expert testimony and evaluate the scientific issues raised in the objections. Subsequently, FDA stayed the regulation (40 FR 56907; December 5, 1975) and delayed the Board's convening while an extensive audit of the authenticity of certain toxicological studies on aspartame was conducted. Of the 15 pivotal studies, 3 were reviewed by an FDA task force and 12 by scientists from Universities Associated for Research and Education in Pathology, Inc. (UAREP), a consortium of 9 universities. Following the finding by UAREP that the animal studies were authentic, the Board convened a public hearing; it completed the hearing and issued its report in 1980 (Aspartame, Decision of the Public Board of Inquiry, Docket No. 75F-0355) (Board's decision).

In the FEDERAL REGISTER of July 24, 1981 (46 38285), the Commissioner of Food and Drugs reviewed the Board's conclusions, and announced his final decision

that aspartame was safe within the meaning of section 409(c) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348(c)). The Commissioner specifically determined that, on the basis of available data, aspartame consumption would not cause brain damage such as mental retardation, brain lesions, or endocrine dysfunction, nor would it cause brain tumors. FDA then reinstated the original regulation (46 FR 50947; October 16, 1981), approving aspartame for the following uses as a sweetener: dry sugar substitutes in free-flowing and tablet form; cold cereals; chewing gum; and dry bases for beverages, instant coffees and teas, puddings and gelatins, and dairy analog toppings (21 CFR 172.804(c)). None of the parties who originally requested a hearing on the regulation objected to or sought judicial review of the agency's final decision to reinstate the regulation approving the dry uses of aspartame.

II. ASPARTAME FOR USE IN CARBONATED BEVERAGES

A. Regulation Approving Use

In the FEDERAL REGISTER of July 8, 1983 (48 FR 31376), FDA issued a final rule that amended § 172.804 by adding new paragraph (c)(6) to permit the additional use of aspartame as a sweetener in carbonated beverages and carbonated beverage syrup bases. That regulation responded to a petition filed by G.D. Searle & Co. (47 FR 46140; October 15, 1982). Before approving this new use, the agency reviewed, among other safety issues, the potential neurotoxicity of the components and decomposition products of aspartame, the stability of aspartame in carbonated beverages, and the potential impact on health of increased consumption of aspartame resulting from its additional use in carbonated beverages.

In the preamble to the final rule, FDA also considered and responded to a number of safety issues raised in comments on the carbonated beverage petition (48 FR 31376 at 31378-31381). These comments expressed particular concern about potential adverse effects of aspartame's component amino acids on the brain, and the potential for exposure to toxic levels of decomposition products, including methanol, from aspartame's use in carbonated beverages. FDA based its approval of aspartame for use in carbonated beverages on its evaluation of clinical studies which were submitted by the petitioner to supplement animal study data supplied with the dry uses petition, data from other relevant studies in the scientific literature, and data contained in comments submitted on the petition (*id.*). These data are all included in the administrative record of Docket No. 82F-0305.

B. Objections and Requests for a Hearing and a Stay

Two objections were filed to the July 8, 1983 regulation approving the use of aspartame in carbonated beverages. The objections contended that numerous safety issues had not been adequately considered by the agency before the promulgation of the regulation, and requested that the regulation be stayed pending examination of those issues in a public hearing. The two parties objecting to the regulation on the basis of unresolved safety issues were James S. Turner, 1424 16th St. NW., Washington DC 20036, objecting on behalf of himself and the Community Nutrition Institute, 1146 19th St. NW., Washington, DC 20036; and Woodrow C. Monte, Director, Food Science and Nutritional Laboratories, Arizona State University, Tempe, AZ. In addition, Richard J. Wurtman, Massachusetts Institute of Technology, Cambridge, MA, commented on the regulation, but did not request a hearing or

a stay of the regulation. Before publication of the final rule approving the use of aspartame in carbonated beverages, Dr. Wurtman wrote a series of letters to FDA in which he expressed his concern about potential adverse effects on brain function of ingesting high levels of carbohydrate and aspartame, and reported the results of some experiments conducted in his laboratory.

FDA denied the requests to stay the effectiveness of the carbonated beverage regulation (48 FR 52899; November 23, 1983), because the public interest did not require it. FDA briefly evaluated each contention of the objections, and concluded that they failed to create doubts about the safety of aspartame significant enough to stay the regulation approving the use of aspartame in carbonated beverages. In that document, FDA also confirmed July 8, 1983, as the effective date of the regulation authorizing the use of aspartame in carbonated beverages.

C. Standard for Granting a Hearing and Character of the Objections

Section 409(f) of the act provides that any person adversely affected by a final food additive regulation may file objections, specifying with particularity the provisions of the order "deemed objectionable, stating reasonable grounds therefor," and request a public hearing based upon such objections. However, the Commissioner may deny the hearing request if the objections to the regulation do not raise genuine and significant issues of fact that can be resolved at a hearing. Specific criteria for determining whether a request for a hearing has been justified are codified at 21 CFR 12.24(b). The pertinent criteria in 21 CFR 12.24(b) for granting a hearing are:

(1) There is a genuine and substantial issue of fact for resolution at a hearing. A hearing will not be granted on issues of policy or law.

(2) The factual issues can be resolved by available and specifically identified reliable evidence. A hearing will not be granted on the basis of mere allegations or denials or general descriptions of positions and contentions.

(3) The data and information submitted, if established at a hearing, would be adequate to justify resolution of the factual issue in the way sought by the person. A hearing will be denied if the Commissioner concludes that the data and information submitted are insufficient to justify the factual determination urged, even if accurate.

(4) Resolution of the factual issue in the way sought by the person is adequate to justify the action requested. A hearing will not be granted on factual issues that are not determinative with respect to the action requested, e.g., if the Commissioner concludes that the action would be the same even if the factual issue were resolved in the way sought * * *.

A party seeking a hearing is required to meet a "threshold burden of tendering evidence suggesting the need for a hearing." *Costle* v. *Pacific Legal Foundation,* 445 U.S. 198, 214-215 (1980) *reh. den.* 446 U.S. 947 (1980), citing *Weinberger* v. *Hynson, Westcott & Dunning Inc.,* 412 U.S 609, 620-621 (1973). An allegation that a hearing is necessary to "sharpen the issues" or "fully develop the facts," does not meet this test *Georgia Pacific Corp.* v. *U.S. E.P.A.,* 671 F.2d 1235, 1241 (9th Cir. 1982). If a hearing request fails to identify any evidence that would be the subject of a hearing, there is no point in holding one. In judicial proceedings, courts are authorized to issue sum-

mary judgment without an evidentiary hearing whenever they find that there are no material issues of fact in dispute and a party is entitled to judgment as a matter of law. See Rule 56, Federal Rules of Civil Procedure. The same principle applies in administrative proceedings.

A hearing request must not only contain evidence, but that evidence should raise a material issue of fact concerning which a meaningful hearing might be held. *Pineapple Growers Association* v. *FDA,* 673 F.2d 1083, 1085 (9th Cir. 1982) (where the issues raised in the objection are, even if true, legally insufficient to alter the decision, the agency need not grant a hearing). *Dyestuffs and Chemicals, Inc.* v. *Flemming,* 271 F.2d 281 (8th Cir. 1959) *cert. denied,* 362 U.S. 911 (1960). FDA need not grant a hearing in each case where an objection submits additional information or posits a novel interpretation of existing information. See *United States* v. *Consolidated Mines & Smelting Co.,* 455 F.2d 432 (9th Cir. 1971). Stated another way, a hearing is justified only if the objections are made in good faith and if they "draw in question in a material way the underpinnings of the regulation at issue." *Pactra Industries* v. *CSPC,* 555 F.2d 677 (9th Cir., 1977). Finally, courts have uniformly recognized that a hearing need not be held to resolve questions of law or policy. See *Citizens for Allegan County, Inc.* v. *FPC,* 414 F.2d 1125 (D.C. Cir. 1969); *Sun Oil Co.* v. *FPC,* 256 F.2d 233, 240 (5th Cir.), *cert. denied,* 358 U.S. 872 (1958).

Even if the objections raise material issues of fact, FDA need not grant a hearing if those same issues were adequately raised and considered in the earlier aspartame proceeding leading to the approval of aspartame for dry uses. Once an issue has been so raised and considered, a party is estopped from raising that same issue in a later proceeding without new evidence. It is illogical not to recognize that the various judicial doctrines dealing with finality can be

validly applied to the administrative process. In explaining why these principles "self-evidently" ought to apply to an agency proceeding, the D.C. Circuit wrote:

> The underlying concept is as simple as this: Justice requires that a party have a fair chance to present his position. But overall interests of administration do not require or generally contemplate that he will be given more than a fair opportunity.

Retail Clerks Union, Local 1401, R.C.I.A. v. NLRB, 463 F.2d 316, 322 (D.C. Cir. 1972). See *Costle* v. *Pacific Legal Foundation, supra* at 1106. See also *Pacific Seafarers, Inc.* v. *Pacific Far East Line, Inc.,* 404 F.2d 804 (D.C. Cir. 1968).

In sum, a hearing request should present sufficient credible evidence to raise a material issue of fact which has not already been the subject of an administrative hearing. As is detailed in section III below, the hearing requests of Mr. Turner and Dr. Monte either do not present sufficient credible evidence to warrant a hearing or, where credible evidence is presented, even if true, that evidence does not raise a material issue of fact. Moreover, the hearing request of Mr. Turner, who was a participant in the hearing on the dry uses of aspartame, raises substantially the same objections that he had presented in the administrative hearing on the dry uses of aspartame. Those issues were considered by the Board's decision at p. 2 and reviewed in the Commissioner's decision (46 FR 38285), and Mr. Turner did not seek judicial review or administrative reconsideration of the agency's final approval for the dry uses of aspartame. Mr. Turner has thus had a fair opportunity to present his position on these issues and an additional hearing on the same issues is unwarranted.

III. ANALYSIS OF THE OBJECTIONS

A. Introduction

This section examines the specific issues identified in the objections to the regulation approving the use of aspartame in carbonated beverages. This document deals with each issue, but certain of the issues are considered at greater length because they have not been covered as extensively in public documents. Similar issues have been combined for ease of discussion and analysis. The general categories are: brain damage, decomposition products, consumption levels, cancer, interpretation of data from clinical studies, quality of data, and labeling. In responding to the various issues raised by the objections, the agency incorporates by reference all materials in the administrative record (Docket Nos. 75F-0355 and 82F-0305).

B. Brain Damage

1. *Brain lesions and mental retardation.* Mr. Turner's objection has expressed concern about aspartame's potential for causing mental retardation, brain lesions, and other adverse behavioral and physiological effects, because of adverse responses to its component amino acids, phenylalanine and aspartate. The issue was raised by Mr. Turner (p. 2) at the hearing on the dry uses of aspartame and was fully considered by the Board and the Commissioner. Thus, further hearing on this issue is unwarranted. The following discussion summarizes the agency's consideration of this brain damage issue and explains the basis for the agency's conclusion that aspartame has been shown to be safe.

Because the phenylalanine and aspartate constituents of aspartame are also constituents of normal dietary protein,

any risk from aspartame ingestion would occur because of the exposure to these amino acids in excess of normal exposure from dietary sources.

Very high doses of aspartate given by gavage or injection have been associated with discrete lesions in the brains of rodents. However, when the same high levels of aspartate or aspartame are administered in the diet to rodents, plasma levels of aspartate do not reach the concentrations required to produce lesions in rodent brains (46 FR 38285 at 38287). Continuous, extremely high plasma levels of phenylalanine, the other constituent amino acide of aspartame, have been known to produce mental retardation in the fetus of phenylketonuric mothers and in infants with phenylketonuria (PKU). However, an adequate margin of safety exists between the levels of phenylalanine known to produce mental retardation and those resulting even from exaggerated exposure to aspartame in carbonated beverages.

The possibility of brain lesions and mental retardation resulting from the use of aspartame was one of the major issues raised by Mr. Turner in his objection to the regulation approving the dry uses of aspartame and was fully considered at the hearing. The Board concluded that the ingestion of aspartame at levels that would be higher than those expected from consumption of aspartame for dry uses and in carbonated beverages could not be expected to increase the incidence of mental retardation, brain damage, or dysfunction of neuroendocrine regulatory systems (Board's decision at p. 39). Subsequently, the Commissioner again reviewed the available evidence regarding brain lesions in rodents associated with aspartate and mental retardation related to phenylalanine. The Commissioner concluded that an adequate margin of safety exists between the amino acid levels resulting even from exag-

gerated exposure to aspartame and those observed to produce brain lesions in the rodent and mental retardation in PKU-related conditions (46 FR 38285 at 38288).

This issue has already been thoroughly considered in the earlier proceeding leading to the approval of aspartame for dry uses and Mr. Turner was given a full and fair opportunity to present his views in the earlier proceeding. Moreover, Mr. Turner could have sought judicial review or administrative reconsideration of the Commissioner's decision on this point, but did not challenge it. Accordingly, he is now estopped from raising the issue without new evidence unavailable at the time of the earlier proceeding. His objection presents no new information on this issue. A hearing is not justified if no data and information are submitted to support the factual determination urged (21 CFR 12.24(b)(3)).

2. *Potential adverse behavioral effects.* The amino acids, phenylalanine, tyrosine (a metabolite of phenylalanine), and tryptophan serve as precursors in the biosynthesis of neurotransmitters in both the periphery and the brain. According to the objections (Turner, p. 4; Monte, p., 5), the data submitted by Dr. Wurtman require the agency to hold a hearing to determine whether aspartame ingestion may alter the brain levels of these precursor amino acids and, in turn, neurotransmitter function, thereby leading to potentially adverse behavioral effects.

Although theories have been postulated to correlate changes in neurotransmitter function with cognitive or affective behavior, the state-of-the-art is such that little definitive evidence is available to support such relationships.

The data submitted by Dr. Wurtman (Ref. 1) in his comments on the carbonated beverage petition demonstrate

increases in the plasma amino acid concentrations of phenylalanine and tyrosine in the human and rat following administration of large doses of aspartame to fasted subjects. The same data also demonstrate increases in the concentration of phenylalanine and tyrosine in the brain of the rat. Dr. Wurtman asserts that these increases in brain tyrosine and phenylalanine might result in changes in catecholamine neurotransmitters synthesized from these precursor amino acids. Drs. Wurtman (Ref. 2) and LaChance (Ref. 3) submitted comments that also postulated that these potential changes in neurotransmitters might lead to unpredictable behavioral effects, but submitted no evidence that would demonstrate that such behavioral effects have been observed or that they might plausibly be anticipated other than on the basis of the theories presented.

In the final regulation approving the use of aspartame for use in carbonated beverages, FDA discussed the data submitted by Drs. Wurtman and LaChance and the related literature on neurochemistry and behavior, and concluded that exposure to aspartame in foods would not result in adverse behavioral effects (48 FR 31376 at 31379-31380). After FDA had approved the use of aspartame in carbonated beverages, Dr. Wurtman submitted additional data in which he measured the levels of rat brain serotonin (5-HT) and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) (Ref. 1). An increase in 5-HT and 5-HIAA occurring after high levels of glucose intake in fasted rats was blocked by concurrent administration of a high dose of aspartame. Dr. Wurtman suggested that this inhibition or "blockade" of glucose-mediated increases in brain levels of 5-HT and 5-HIAA by very high doses of aspartame, which he observed in animal studies, might mean that consumption of aspartame by humans

could interfere with their normal pattern of carbohydrate consumption. Dr. Wurtman did not provide any evidence that the observed changes in brain 5-HT and 5-HIAA levels produced a change in the eating habits, preferences, or any other behavior of the animals tested.

FDA has reviewed the data dealing with the effect of aspartame in glucose-mediated changes in brain neurotransmitters that were submitted and has concluded that they are consistent with expected results following simultaneous administration of any food containing protein with glucose. The findings represent normal physiological variations in brain neurochemicals, which are a response to a specific dietary regimen, and thus would not be expected to be associated with adverse behavioral effects.

Drs. Wurtman and LaChance have developed interesting, but untested, hypotheses. The hypotheses do not, even if true, suggest that aspartame is not safe; they suggest merely that certain chemical changes may occur as the result of ingesting aspartame. For this reason, no purpose would be served by holding a hearing, because no issue of material fact is raised by the hypotheses. Moreover, even if the hypotheses raised an issue of material fact, a hypothesis, standing alone, does not justify a hearing in the absence of data on which to base a resolution of the issue raised. No such data are identified in Dr. Wurtman's submission or in the objections. FDA, therefore, denies the request for a hearing on these issues.

C. Decomposition and Reaction Products

There is a customary battery of toxicological tests in various animal species that is required to demonstrate the safety of a direct food additive. These tests generally are

familiar to sponsors of food additive petitions. To disseminate information about these tests further, the agency has developed and published a set of publicly available guidelines describing these tests "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food" ("REDBOOK" (Ref. 4)). The "REDBOOK" also sets forth certain tests beyond the customary battery of tests that the agency requires if the chemical structure of the additive or some other factor suggests particular reasons for concern.

In support of its petition for the use of aspartame for dry uses, Searle performed a complete series of traditional toxicological studies involving laboratory animals to verify the safety of aspartame during chronic exposure (Ref. 5). The design of the studies meets or exceeds that stated in the "REDBOOK" guidelines. In addition, because a consumer could be exposed to signficant quantities of aspartame on a daily basis, and occasionally to high levels of aspartame, the petitioner conducted clinical studies (studies in humans) that provided ample evidence of the safety of aspartame under predicted levels of chronic ingestion or unusual situations of high, acute exposure (Refs. 6 and 7).

Before FDA approved aspartame, Searle submitted, and FDA evaluated, more than the usual tests with respect to the decomposition of this food additive. Because it is not feasible to require manufacturers to test every decomposition product, the agency routinely does not require testing of all of them unless a particular decomposition product poses a safety question, or little is known about its toxicological profile.

With respect to the toxicity of diketopiperazine (DKP), a primary decomposition product of aspartame, Searle submitted data in support of its petition for aspartame's

dry uses to establish DKP's safety (Ref. 8). The agency also anticipated that a safety problem might arise in the use of aspartame in carbonated beverages if DKP, in solution, formed nitrosamines. Accordingly, Searle submitted, and FDA evaluated, studies on the likelihood of nitrosamine formation from the use of aspartame in carbonated beverages (Ref. 9).

FDA was aware of significant scientific literature on the toxicity of the following components of aspartame: phenylalanine, aspartic acid, and methanol. The agency reviewed the safety data submitted by Searle in support of its petition for dry uses derived from animal and clinical studies and consumption studies, as well as the existing body of scientific data, and concluded that the studies demonstrated the safety of these components. The Board's decision at p. 20 and p. 38 and the Commissioner both concluded that these components are safe (46 FR 38285 at 38287).

The objections now contend that FDA has failed to dispose of the possibility that decomposition and reaction products created by the addition of aspartame to carbonated beverages and carbonated beverages syrup bases may make those products unsafe (Turner, II, p. 9).

1. *Unidentified and unsafe decomposition and reaction products.* The objections present no evidence to support their contention that unidentified decomposition products or reaction products of aspartame may be harmful (Turner, p. 9; Monte, p. 8). One objection refers to an abstract of a scientific talk which discusses the reactivity of aspartame with certain flavor components of food (aldehydes and ketones) (Monte, p. 9). Reactions between food components occur too commonly to warrant specific testing for each individual class of reaction or decomposition products. Food itself undergoes a number of reactions, for

example, in cooking. As the agency pointed out in the final regulation approving the use of aspartame in carbonated beverages, the similarity of the basic dipeptide structure of aspartame to normal dietary protein provides an added measure of assurance of its safety in regard to reactivity with food components and its metabolic fate (48 FR 31376 at 31382). Because the objection has presented no data to support its concern, and because the agency has no independent basis for concern, there is no basis upon which to grant a hearing. The agency will not grant a hearing on the basis of mere unsubstantiated allegations. Further, in the absence of any data, the simple charge that there may be a safety issue regarding decomposition products calls into question the agency's policy regarding the threshold for requiring scientific testing of such products. This question is one of both policy and law, i.e., the proper legal interpretation of the safety standards of the act, and thus is not a proper issue for an evidentiary hearing.

2. *Inability to account for up to 30 percent of the sweetener.* The objection states that Searle is unable to account for as much as 30 percent of the sweetener, despite having analyzed for components expected in the usual breakdown pathways, and that a more complete breakdown occurs at temperatures above 30° C (86° F) (Turner, p. 10). As detailed in the preamble to the carbonated beverage rule, the petition for this use of aspartame included the results of extensive stability studies on carbonated beverages (48 FR 31376 at 31377). These experiments were performed with beverages stored at various temperatures for periods of up to 52 weeks. Four beverage flavors were analyzed for aspartame and five decomposition products at various intervals. Essentially all of the analyses of beverages stored at 30° C for up to 40 weeks accounted for 98 to 100 percent of the original added aspartame. The contention

that 30 percent of the decomposition products are unknown is misleading, because it focuses on the results at high temperatures (40° C (104° F); 55° C (131° F)) in which the results of the analysis are not as complete as those at lower temperatures. The more complete breakdown at higher temperatures is not unexpected, and, more important, is not crucial to the determination of the safety of the breakdown products. The sum of the decomposition studies submitted with the aspartame food additive petition for use in carbonated beverages provided the necessary identification of the decomposition products and evidence of their safety. The objections present no evidence in support of the implied increase in risk from greater decomposition at the higher temperature, other than the contention that the decomposition products are "unidentified" and that higher levels of free methanol would be present. After evaluating the studies and the general body of literature on the subject, FDA concluded that there was no reason to believe that the additional decomposition products would be substantially different from those formed at lower temperatures (48 FR 31376 at 31377). The objection does not justify a hearing because it presents no evidence that calls into question the safety of these decomposition products. As discussed above in section III.C.1., the allegation that all decomposition products should be presumed to be unsafe and therefore tested raises a legal and policy issue and is not appropriate for resolution at a hearing. (The toxicity of the decomposition product methanol is discussed below.)

3. *Methanol ingestion from decomposed aspartame.* Both objections argued that aspartame's decomposition can result in exposure to adverse levels of methanol, "a known poison," (Monte, p. 2) and that the metabolism of methanol in the body yields formaldehyde, "a known car-

cinogen" (Turner, p. 12) (see section III.E. below). The agency evaluated the safety issues related to the ingestion of methanol derived from aspartame in its evaluation of aspartame for dry uses and concluded that the levels of methanol resulting from the use of aspartame in carbonated beverages did not pose any safety issues because they were well below levels of exposure expected to product toxicity (Ref. 10).

Dr. Monte's objection argued (1) that "free" methanol produced by the decomposition of aspartame in carbonated beverages is more toxic than "dietary" methanol formed by the metabolism of aspartame in the gastrointestinal tract because of the differences in metabolism and a more complete amount of absorption of "free" rather than "dietary" methanol;' and (2) that the amount of "free" methanol absorbed as a result of aspartame consumption is of sufficient quantity to produce a "significant and rapid rise in methyl alcohol and formate levels in the plasma" (Monte, p. 4). The objections allege that these levels are of toxicological concern under acute or chronic use conditions, but they neither submitted nor referred to available data in support of that allegation.

a. Free Methanol Is Not More Toxic Than Methanol Produced by the Metabolism of Aspartame in the Gastrointestinal Tract

The objection proffered a hypothesis that the decomposition of aspartame to methanol or to any of its secondary metabolites prior to consumption poses additional safety questions regarding the continued use of aspartame in carbonated beverages, but provided no evidence to support that position (Monte, p. 3). FDA analyzed the methanol safety issue before the agency approved aspartame for dry uses and again in its evaluation of the petition for use

in carbonated beverages (Ref. 10). The objection has presented no evidence of any kind to alter FDA's original evaluation. FDA cannot accept as a basis for conducting a hearing unsubstantiated hypotheses concerning issues the agency already satisfactorily resolved.

Metabolic studies performed in monkeys and submitted by Searle in support of its petition for aspartame for dry uses demonstrate that the overall metabolic disposition of the methanol moiety from aspartame is similar to that of methanol administered alone to monkeys (Ref. 11). The methyl moiety appears to be rapidly and completely cleaved from aspartame in the gastrointestinal tract, and this methyl group is oxidized in essentially the same manner as "free" methanol. The only detectable difference in the pharmacokinetic properties between "free" methanol and "dietary" methanol derived from the hydrolysis of aspartame is a faster rate of absorption of the "free" methanol within the first hour. "Free" menthanol is readily absorbed from the stomach whereas aspartame must pass into the small intestine before hydrolysis and absorption of the methanol can occur. This small difference in the rate of methanol absorption is not significant because the metabolism of methanol is slow and because the overall amount of methanol ultimately absorbed as a result of consumption of a given quantity of aspartame-sweetened beverage is the same.

Thus, there is no scientific basis for differentiating the "free" from the "dietary" methanol in analyzing the toxicological profile of aspartame. The agency evaluated the metabolism data early in its evaluation of the data in support of the dry use petition, and assumed that methanol was completely hydrolyzed from aspartame in the gastrointestinal tract (Ref. 11). Exposure to methanol from aspartame can be calculated on a one-to-one molar basis

independent of the decomposition rate in carbonated beverages, which can vary with storage conditions. Therefore, an estimate of methanol exposure following ingestion of aspartame is provided by taking 10 percent of the weight of the aspartame dose. The objection submits no data that support its position or discredit the agency's conclusions based on the earlier studies performed by Searle. Thus, there is no basis for granting the hearing request.

b. The Amount of Free Methanol Absorbed from Aspartame Does Not Produce a Significant and Rapid Rise in Plasma Methyl Alcohol and Formate Levels

One objection (Turner, p. 11) contended that FDA had incorrectly concluded that the level of dietary exposure to methanol is not of "prime importance" in assessing the safety of aspartame (48 FR 31376 at 31380). The objection did not, however, present evidence showing at what concentration methanol is toxic or that the consumption of aspartame would result in the consumption of toxic levels of methanol.

The agency does not believe that methanol exposure equivalent to 10 percent of the aspartame dose is of sufficient quantity to be of toxicological concern under acute or chronic use conditions. A study (Ref. 12) submitted by Searle in support of its petition for the dry uses of aspartame showed no detectable levels of methanol in the blood of human subjects following the ingestion of aspartame at 34 milligrams per kilogram (mg/kg) body weight (the 99th percentile level of projected ingestion across all age groups). Assuming complete hydrolysis after ingestion, this 34 mg/kg dose of aspartame is equivalent to a dose of 3.4 mg/kg body weight of methanol. The agency reviewed this study and others dealing with methanol toxicity prior to approving aspartame for dry uses and cited the data in

the preamble to the final regulation approving the use of aspartame in carbonated beverages (48 FR 31376 at 31380).

Even following administration of an abuse dose of aspartame of 200 mg/kg body weight (equivalent to 20 mg/kg body weight of methanol or drinking more than 13 quarts of aspartame-sweetened orange soda) in a clinical study conducted by Searle, the mean peak blood methanol concentration reached only 26 mg per litter. The hearing request contains no evidence to suggest that even this level of methanol, consumed in free form, is toxic. Thus even if all aspartame in soft drinks decomposed prior to their consumption, the agency has no reason to believe any danger of methanol poisoning would exist. FDA remains convinced that the studies submitted by Searle in support of the dry uses, and reviewed by FDA prior to the dry use approval and again in its evaluation of the carbonated beverage petition, adequately support the agency's conclusion that there was "no cause for concern from the levels of dietary methanol resulting from the highest projected levels of aspartame consumption" (48 FR 31376 at 31381).

The agency has recently become aware, however, of clinical data that further buttress the agency's determination. Although FDA did not rely on these studies in approving the carbonated beverage petition, nor is it necessary to rely on the studies here, the agency believes that they present pertinent information that is consistent with that contained in the Searle data. This document discusses them to some extent. FDA has placed copies of the reports in the administrative record for Docket No. 82F-0305. Among these studies are some that indicate that the toxic effects of methanol are due to formate accumulation and not to formaldehyde or methanol itself (Refs. 13, 14, and 15). Formate is the oxidation product of formaldehyde

which is itself formed from the metabolism of methanol. In the Searle clinical study using abuse doses of aspartame equivalent to 20 mg/kg body weight of methanol, no significant increases were observed in plasma concentrations of formate, suggesting that the rate of formate production does not exceed its rate of urinary excretion. In fact, studies in human subjects given oral dosages of methanol of 71 to 84 mg/kg body weight showed no toxic effects with blood levels of methanol reaching 47 to 76 mg per liter 2 to 3 hours afterwards (Ref. 16). From estimates based on blood levels in methanol poisonings, it appears that the ingestion of methanol on the order of 200 to 500 mg/kg body weight is required to produce a significant accumulation of formate in the blood which may produce visual and central nervous system toxicity (Refs. 17 and 18).

The toxic doses of methanol (200 to 500 mg/kg body weight) are approximately one hundred times that ingested when aspartame is consumed at the 99th percentile level of projected chronic ingestion (10 percent of 34 mg/kg body weight aspartame, or 3.4 mg/kg body weight methanol). Moreover, orange soda, which may contain the highest concentration of aspartame in carbonated beverages (335 mg aspartame per 12 fluid ounces or 930 mg per liter), results in a lower methanol level (93 mg per litter) than that found in the average fruit juice (140 mg per liter) (Ref. 19). Under the most conservative assumption, the complete hydrolysis of aspartame to methanol, an adequate margin of safety exists for the use of aspartame in carbonated beverages. The consumption of aspartame would not result in toxicologically significant methanol and formate levels.

Finally, it is well known that much food contains

significant quantities of methanol. In fruit juices, the average content of methanol is 140 mg per liter and grain alcohols (such as gin and whiskey) contain as much as 1,000 mg per liter (Ref. 19). Moreover, fresh fruits and vegetables also contain compounds that are metabolized in the body to methanol (Refs. 20 and 21). Normal metabolic processes such as purine and pyrimidine biosynthesis and amino acid metabolism require methyl groups from compounds like methanol (Ref. 22). It also appears that either methanol or formaldehyde may serve as precursors for the methyl groups in choline synthesis (Ref. 23).

The agency has concluded that, because the objection has failed to present evidence establishing at what level methanol is toxic and whether consumption of carbonated beverages containing aspartame would exceed that level, no hearing is required to reevaluate the significance of exposure to methanol from aspartame consumption. The objection submitted no data and the agency is aware of none in support of the objection's position. FDA will not grant a hearing on the basis of a mere allegation.

4. *Nitrosamines formation from DKP and toxicity of DKP.* The objections allege that the agency has "mischaracterized" and "failed to consider" data dealing with potential toxicity from DKP (Turner, p. 10) and has failed to assess the "potential danger" of nitrosamine formation by intestinal bacteria after prolonged exposure to DKP (Monte, p. 7).

a. Nitrosation of DKP

FDA reviewed studies conducted by Searle aimed at evaluating the nitrosation potential of aspartame and DKP before the original approval of aspartame in 1974. These studies attempted to form, under ideal conditions, the

nitrosamines of aspartame and DKP and demonstrated that stable nitrosamine derivatives were difficult to form at a level detectable with the then current analytical methodology (Ref. 24). The study also demonstrated that nitrosamine derivatives of aspartame or DKP intermediates, formed under ideal laboratory conditions, were extremely unstable under physiological or aqueous conditions. Given these results, FDA concluded that it was most unlikely that any nitrosamines could remain in the gastrointestinal tract or in an aqueous solution, such as soft drinks, containing aspartame or DKP (Ref. 25).

The objections further contend that the agency has been remiss in not reexamining the nitrosamine issue, employing more sensitive, modern analytical methodology. In support of this contention, one objection (Monte, p. 7) cites a recent publication describing the low level detection at parts per billion levels of structurally unrelated nitrosamines in malt beverages. The objection offered no evidence that the formation of nitrosamines in malt beverages has any possible relevance to structurally dissimilar nitrosamine formation in soft drinks containing aspartame. Nor did the objection present any evidence to rebut the data submitted by the petitioner that these compounds cannot be readily formed in aspartame. The agency therefore concludes that no hearing is required because the objection did not provide any evidence to refute the previous safety determination on nitrosamine formation. Thus, the objection states an allegation, but raises no issue of fact on which to base a hearing.

b. Toxicity of DKP

An additional issue raised by the objection was that FDA had "mischaracterized" the results from Lederer's

study on DKP and that the agency had "failed to consider adequately the concern" for fetal toxicity (Turner, p. 10). The teratology and reproduction studies conducted by the petitioner in support of its petition for dry uses of aspartame rebut that position (Ref. 25). Moreover, the agency notes that Dr. Lederer acknowledged, prior to the publication of the carbonated beverage rule, that "the conclusions of my work are concordant with those of the U.S.A." (Ref. 26; see also the discussion at 48 FR 31376 at 31380). Consequently, the agency also finds that the objections raise no material issue of fact with regard to potential embryotoxicity, but make an unsupported allegation. FDA will not hold a hearing based on a mere allegation.

D. Consumption Levels

Mr. Turner's objection alleges that in concluding that aspartame was safe for carbonated beverage use, the agency improperly estimated consumption levels of aspartame because (1) FDA failed to include additional individuals likely to consume carbonated beverages; (2) FDA based consumption levels on understated or nonexistent calculations; (3) the use patterns on consumption in the petition were not correct; (4) FDA did not consider the consumption of products containing aspartame at the three main meals; (5) FDA did not include consumption of aspartame in hot weather in the estimate; (6) FDA used the "gross national population consumption formula" to calculate consumption; (7) intake greater than the previous acceptable daily intake is unsafe (Turner, pp. 19-23).

Various consumption estimates, including estimates of aspartame exposure resulting from the consumption of carbonated beverages containing aspartame, were exhaustively considered by the Board's decision at p. 14 to p. 22

and by the Commissioner in his final decision approving aspartame for dry uses (46 FR 38285 at 38289-38290). Mr. Turner argued in the earlier proceeding that the consumption levels were underestimated and the Board and the Commissioner considered but rejected these arguments. Thus, Mr. Turner has been given a full opportunity to present his views on consumption.

FDA believes further that the objection demonstrates a basic misunderstanding of how the agency calculates the estimated daily intake (EDI) of food additives, and how these dietary exposure estimates relate to the acceptable daily intake (ADI) of the additive. The agency is therefore discussing the important principles used to develop consumption estimates.

The EDI is a measure of chronic dietary exposure of the additive from all food sources in which it is used; it is the day-in and day-out estimated intake over a particular span of an individual's lifetime. The ADI is the amount of a compound that can be safely consumed each day on a chronic basis; it is derived primarily from chronic toxicological studies in animals. Levels of consumption may occasionally rise above or fall below the EDI. Daily carbonated beverage consumption, for example, may be greater in hot weather. The important safety issue is whether the EDI exceeds the ADI. Both of these figures may change as chronic consumption patterns change. The EDI will increase as the use of the additive is extended to other food categories, and the ADI may be revised as more toxicological information is evaluated. For example, prior to the approval of the use of aspartame in carbonated beverages, the agency increased the ADI from 20 to 50 mg/kg body weight, because additional toxicological data from clinical studies submitted by the petitioner demonstrated that the new level was safe (Ref. 10).

The allegations that FDA failed to include additional individuals likely to consume carbonated beverages, that carbonated beverage consumption was understated or that consumption calculations do not exist are simply untrue. Searle and FDA calculated the maximum EDI of aspartame during the proceedings leading to the approval of aspartame for dry use and again during the evaluation of the carbonated beverage petition using three different methods. FDA reviewed each of these estimates (46 FR 38285 at 38289; 48 FR 31376 at 31377). Each of the EDI exposure estimates, including the 34 mg/kg body weight estimate ultimately accepted by the Commissioner (46 FR 38285 at 38290), explicitly included aspartame intake from carbonated beverages or was even broader in scope. (See 46 FR 38289-38290 for a complete discussion of consumption levels.) One estimate assumed that aspartame replaced all sucrose in the diet of an average male, and another assumed that aspartame replaced all carbohydrate in that diet.

The objection alleges that the patterns of consumption in the petition were not correct but submitted no data to show that actual use patterns differ from those calculated by Searle and FDA. FDA calculates dietary exposure estimates of new direct food additives by applying data on food consumption, as established by surveys, and data on the concentration of the additive in foods. The data submitted by Searle dealt with all aspects of aspartame consumption including consumption with other foods, such as the three main meals. In its petition for carbonated beverage approval, Searle included a new calculation that relied on the most recent survey data compiled by the Market Research Corp. of America (MRCA). MRCA survey data are compiled from dietary records kept throughout the year by 4,000 U.S.households. Estimates using MRCA

data are based on the foods actually eaten by people in various age brackets and include data from both average and heavy users in particular food categories. Prior to approving aspartame for use in carbonated beverages, the agency reviewed the Searle calculation and computed its own values for aspartame exposure from all foods (Ref. 27). The agency's evaluation specifically recorded the percentage increases in estimated aspartame exposure resulting from carbonated drink consumption, and concurred with the petitioner's method of calculation, but restated the exposure estimate to reflect "eaters only." This estimate of EDI is based on those people who actually consume the product and maximizes EDI figures for any particular age group, because it does not average in the nonconsumer in the survey population.

On an occasional day, for example in hot weather, intake levels of aspartame may exceed the ADI. However, this occasional excess would not result in chronic intake above the ADI. Whether it is safe to ingest levels of a substance on some days in excess of the established ADI depends on how acutely toxic the additive is. Clinical tests of aspartame at doses of 200 mg/kg body weight, which exceeds the ADI, were performed and submitted by Searle in support of its petition (Ref. 6). In these studies, the acute effect of the ingestion of single doses of 200 mg/kg of aspartame on blood levels of amino acids and methanol were found to be well below toxicological levels of concern (48 FR 31376 at 31381). Thus, Mr. Turner's observation that the consumption of six cans of beverage containing aspartame on a hot day will result in exposure that exceeds the ADI is not a credible basis for alleging that the agency has "understated" consumption levels (Turner, p. 21). The consumption by a 20 kg child of six 12-ounce cans of orange beverage sweetened with aspartame would result in

an exposure of 100 mg/kg of aspartame, which is well below the 200 mg/kg dose administered in Searle clinical study without any sign of acute toxicity (Ref. 6) and even further below the levels of toxicological concern. (Six 12-ounce cans of orange beverage sweetened with aspartame (.93 mg per milliliter) would contain approximately 2,008 mg of aspartame.) Accordingly, the objection fails to present credible evidence raising a material issue of fact. The objection is also based on a demonstrably false premise.

As discussed above, the agency has estimated that the highest likely chronic consumption of aspartame per day would be 34 mg/kg body weight. The objection contended that aspartame consumption will not always occur in a "throughout the day" pattern, but would occur principally in large doses, that is, at meals when individuals are most likely to consume food and aspartame-containing beverages at the same time (Turner, p. 20). The agency does not regard the possible consumption of aspartame in a single large dose as posing any safety problem whatsoever. During the evaluation of the petition for the dry uses of aspartame, the agency analyzed the toxicity from acute exposure to aspartame. FDA relied upon a study in which high single doses of up to 200 mg of aspartame per kg of body weight were given to human subjects (Ref. 6). With respect to acute toxicity, the pattern of aspartame ingestion over the day is not important as long as the total amount ingested per day does not exceed the 200 mg/kg level shown to be safe.

Finally, FDA is not familiar with the term "gross national population consumption formula" mentioned in the objection and is unable to determine its relevance to the issue of aspartame consumption (Turner, p. 22). Presumably, the objection is suggesting that FDA should

adopt an entirely new policy regarding estimates for food additive consumption instead of its current policy, which is described above and is used in estimating the projected consumption of food additives. The current policy and possible alternatives to it are not at issue in this proceeding, nor are they proper issues for a formal evidentiary public hearing. Moreover, the objection presents no evidence describing this proposed new consumption formula, or establishing its validity.

FDA is denying the request for a hearing on the consumption issue for a number of reasons. First, Mr. Turner was a party to the earlier proceeding in which consumption estimates were an important issue. He raised essentially the same consumption issue there. The Board's decision at p. 14 to p. 22 and the Commissioner's decision (46 FR 38285 at 38307) each discussed the matter and ruled against Mr. Turner's objection. Mr. Turner could have sought judicial or administrative review of the earlier decision. He did not do so. He cannot now complain, because he has had a full and fair opportunity to present his views and be heard. Moreover, his objections present no data in support of his position.

E. Carcinogenicity Potential of Aspartame and its Metabolites

1. *Aspartame's potential for causing brain tumors.* Mr. Turner objects to the approval of aspartame for use in carbonated beverages because "the Commissioner and the agency have not adequately dealt with the recommendation of the Public Board of Inquiry that approval of aspartame be withheld pending results from further oncogenic studies with the additive" (Turner, p. 15). Interpretation of the results of the chronic rat feeding studies designed to

determine aspartame's potential for causing brain tumors was one of the major scientific issues before the Board, and consequently one of the most comprehensively deliberated issues bearing on aspartame's safety. The Board found that the results of these tests were not sufficiently conclusive and recommended that approval of aspartame be withheld pending results from further oncogenic studies with the additive (Board's decision at p. 49). The Commissioner disagreed with the Board's findings and concluded that there was a reasonable certainty that aspartame does not cause brain tumors in rats (46 FR 38285 at 38295). Mr. Turner was a party to that earlier proceeding and made the same objection to the regulation approving dry uses of aspartame. He received a formal hearing on that objection. Mr. Turner now contends that the Board's findings, rather than the Commissioner's findings, were correct. Mr. Turner's current objection did not, however, submit any new data on this issue.

In his final decision (46 FR 38285 at 38295), the Commissioner explained why he disagreed with the Board's findings that more studies were needed on the carcinogenic potential of aspartame. This decision is supported by the record which included not only the three chronic studies before the Board but also negative results observed in a subsequent animal study not available to the Board (Ref. 28).

The administrative record shows that the approval of aspartame is supported by a complete series of toxicological tests in animals. These studies have been thoroughly reviewed by FDA scientists. Based on that review and for the reasons stated in the Commissioner's decision, the agency reaffirms the conclusion that there is a reasonable certainty that aspartame does not cause brain tumors in rats.

Mr. Turner had a fair opportunity to present his arguments and have them fully considered in the proceeding leading to the approval of aspartame for dry uses. He had an opportunity to challenge the Commissioner's decision in the Court of Appeals. He chose not to do so, and is thus estopped from relitigating the issue in the absence of new evidence. He has presented no new evidence in support of his position here, and thus has raised no material issue of fact that justifies a further hearing in this proceeding.

2. *Uterine polyps in rats.* Mr. Turner's objection states that "* * * neither the Commissioner nor the agency has recognized 'precancerous polyps' in the approval of aspartame for use in carbonated beverages" (Turner, p. 34). The polyps in question originated in the uteri of rats chronically administered the diketopiperazine-derivative of aspartame (DKP) for 2 years (Ref. 29). The study data in question were submitted to the agency in support of Searle's original food additive petition for aspartame. Subsequently, as a result of FDA's concern over the issue, the agency referred the raw data to four independent teams of pathologists at FDA, the Massachusetts Institute of Technology, the Armed Forces Institute of Pathology, and F.D. Searle for review. Prior to convening the Board, those teams identified cystic endometrial hyperplasia, which is commonly referred to as uterine polyps, as the most common lesion. Cystic endometrial hyperplasia occurs in aging rats spontaneously and is most commonly associated with age-related endocrine disturbances. Uterine polyps are considered to be a localized form of endometrial hyperplasia and have no tendency to undergo malignant transformation and, therefore, are not considered precancerous in nature (Ref. 30).

The Searle study also supports a safety factor of about 1,000 with respect to the induction of uterine polyps. Thus, the agency concludes that the possibility that uterine polyps will occur as the result of aspartame ingestion is very remote (Ref. 29).

Because the polyps were not considered precarcinogenic, they were not an issue specifically addressed by the Board and the Commissioner. Nonetheless, Mr. Turner could have raised the issue at the hearing or before the Commissioner. He could have sought judicial review of the Commissioner's decision, but did not. He has had an adequate opportunity to be heard.

3. *Carcinogenic potential of formaldehyde.* The objections stated that there are no studies available for FDA to use in assessing the chronic toxicity and carcinogenic potential of methanol and formaldehyde formed from methanol metabolism in the body (Monte, p. 4; Turner, p. 12).

The Agency does not agree with this assertion. In its original submission to FDA in support of the use of aspartame for dry uses, Searle included the results of chronic feeding studies of aspartame in the dog, the mouse, and the rat (Ref. 31). The results of another chronic study that corroborate the Searle study are available through the open literature (Ref. 28). One of the major objectives of this type of chronic study is a comprehensive histopathological examination of virtually all organ systems in order to assess both the chronic toxic and carcinogenic potential of the administered compounds.

Before approving the original petition for aspartame for dry uses, FDA analyzed the chronic feeding studies and concluded that aspartame was safe. Although these studies were designed to assess the toxicity and potential car-

cinogenicity of aspartame, they also tested the toxicity and potential carcinogenicity of aspartame's metabolites. The metabolic studies submitted by the petitioner demonstrate that all ingested aspartame is broken down in the gastrointestinal tract into its constituents, aspartic acid, phenylalanine, and methanol. Because the aspartame molecule is 10 percent methanol by weight and because the dosages used in the chronic studies were quite high (rat: 1 to 8 g/kg body weight, mouse: 1 to 4 g/kg body weight, and dog: 1 to 4 g/kg body weight), the exposure of these species to methanol in these four chronic studies was as high as 400 to 800 mg/kg body weight per day, a very significant dose. Based on an ADI for human exposure of 50 mg of aspartame per kg body weight per day (or 5 mg/kg body weight of methanol), these doses represent an 80- to 160-fold exaggeration of methanol exposure in the chronic animal studies when compared with the very high but conceivable levels of human exposure to methano through aspartame ingestion.

The Searle studies also ensured comparable dosages and durations of exposure to formaldehyde, because, as discussed above, methanol is metabolized to formaldehyde on a one-to-one molar basis. Thus, contrary to the objections, both methanol and formaldehyde were thoroughly tested, and FDA reviewed the results of those tests prior to approving aspartame for dry uses.

The hearing request cites a recent study indicating that formaldehyde, administered intranasally to rats, produced carcinomas at the site of application — the nasal turbinates (Ref. 32). The site of the carcinomas strongly indicates that the neoplastic process is a localized, not a systemic, reaction to the known irritating and cytotoxic properties of formaldehyde. No increase in tumor incidence was observed at sites remote to direct exposure

(Ref. 32). The same study supports the further conclusion that direct exposure to relatively high concentrations of formaldehyde gas is necessary before the carcinogenic process occurs.

In addition, there is another series of chronic studies in the scientific literature, which FDA considered prior to the approval of aspartame for dry uses, in which hexamethylenetetramine was administered in the drinking water in doses of 0.5 to 5 percent to three strains of mice for 60 weeks and to Wistar rats in drinking water at 1 percent for 104 weeks (Ref. 33). Because hexamethylenetetramine is broken down in the acid medium (Ref. 34) of the stomach to formaldehyde, these studies directly tested whether orally administered formaldehyde is carcinogenic (Ref. 33). In the hexamethylenetetramine studies, no evidence of carcinogenic activity was found in any of the test groups.

The fact that aspartame when ingested in doses up to 8 gm/kg body weight (800 mg/kg formaldehyde) produced no carcinogenic effect is strong evidence that formaldehyde exposure from the oral route of administration is without carcinogenic risk. Any question regarding adequacy of dosing from these studies is resolved by the results from the studies with hexamethylenetetramine where doses of up to 1,500 mg/kg body weight formaldehyde were ingested by mice and rats without any carcinogenic effect. Thus, the inhalation study is not appropriate for use in determining whether formaldehyde is a systemic carcinogen and in evaluating the safety of aspartame. There is no issue of fact, because it has been demonstrated that formaldehyde is not a systemic carcinogen. No hearing is required, because the objection does not submit sufficient evidence to raise a serious question about aspartame's systemic carcinogenicity. Although

the agency does not believe that a hearing is justified in view of the hexamethylenetetramine studies, the objectors may request reconsideration as provided in 21 CFR 10.33 and are free to submit comments on the hexamethylenetetramine studies, or on any other studies that are or may become available.

4. *Two human cancers in clinical studies.* One of the objections claims that the Commissioner failed to assign sufficient significance in his decision approving aspartame for dry uses to the finding of two human cancers at the eleventh week of a 13-week study on aspartame (Turner, p. 17). One insulin-dependent diabetic developed an adenocarcinoma of the breast and one non-insulin-dependent diabetic developed a reticulosarcoma of the stomach.

The agency as well as a reviewing pathologist concluded that these types of cancer are associated with a pathological process requiring many months to years for development into a malignant phase. Therefore, the cancers arising in these two patients receiving aspartame were considered to be coincidental and unrelated to aspartame intake.

As with so many of Mr. Turner's objections, that issue was before the Board and the Commissioner in the earlier proceeding. Mr. Turner could have appealed the Commissioner's decision. That he chose not to do so means that he may not raise the issue again at this time. He has had an adequate opportunity to be heard, and no new hearing is required.

F. Interpretation of Data from Clinical Studies

Mr. Turner's objection alleges that FDA failed to give adequate credence to the potential for adverse reactions related to the use of aspartame observed in the clinical studies (Ref. 35). The objection pointed out that there were five times as many complaints reported by aspartame users as by the control group in that study (Turner, p. 22).

FDA did evaluate these results. The clinical study referred to in the objection was only one of several clinical studies, which included normal adults and children, as well as obese and diabetic adults, conducted by the petitioner and submitted to the agency in support of its petition on dry uses of aspartame (Ref. 7). Based on an analysis of the results from all these studies, FDA concluded that there was no evidence of any consistent or obvious pattern of specific complaints from aspartame use.

All the data from these studies were available prior to the earlier hearings. Mr. Turner could have raised the issue at the hearing or before the Commissioner but did not do so. He has had an adequate opportunity to be heard, and no hearing is required on the issue. Moreover, in the absence of any additional data bearing on the clinical study, Mr. Turner's objection constitutes nothing more than an allegation, and raises no material issue of fact upon which a hearing could be held.

G. Quality of Data

One objection claims that the research submitted by G.D. Searle should not have been relied upon for evaluating the safety of aspartame because the research was conducted in a flawed and inaccurate manner (Turner, p. 23). This issue was presented to the Commissioner in the earlier proceeding on the dry uses of aspartame and although

decided adversely to Mr. Turner, he failed to seek judicial or administrative review of the issue. Although Mr. Turner is estopped from relitigating this issue a second time, the agency has nevertheless considered it and concluded that the quality of the data is adequate.

The agency believes that there has been an adequate confirmation of the quality of the studies to provide reliable evidence for the safety assessment of aspartame. In fact, a comprehensive review of the authenticity of the aspartame research data was performed on the 15 pivotal studies submitted by G.D. Searle. Three of these studies were audited by FDA and 12 by UAREP. This was a massive undertaking and took over 2 years to complete. UAREP concluded that the studies were authentic and, on December 13, 1978, submitted to FDA its 1,062 page report. The agency agreed with UAREP that those 12 studies, as well as the 3 studies which it had reviewed, were indeed authentic. In addition to determining the authenticity of these studies, the report by UAREP also contained detailed observations of how these studies were conducted.

Although UAREP, like the agency, noted some procedures and irregularities that warranted improvement, none were of such a serious nature as to invalidate an entire study. In view of the fact that the objection has provided no new information on the quality or design of Searle's data, the agency believes that it is adequately addressed in the Commissioner's final decision on aspartame (46 FR 38285 at 38301).

H. Labeling of Food Containing Aspartame

One objection contends that foods containing aspartame are not adequately labeled, but provides no information to

support the position that current requirements are insufficient (Monte, p. 10). Current regulations require that the label of any food containing aspartame shall bear a prominent and conspicuous notice to phenylketonurics that the product contains phenylalanine.

No other susceptible consumer group has been identified by the objection, nor has it identified the "substantial dangers" (Monte, p. 10) posed by the regulated uses of aspartame. Accordingly, the agency concludes that the issue raised is one of policy, not fact, and is not resolvable by a hearing.

V. SUMMARY AND CONCLUSIONS

Under 21 CFR 170.3(i), the safety of a food additive means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. FDA's regulations reflect the Congressional judgment that the additive must be properly tested and the tests carefully evaluated, but the additive need not, indeed cannot, be shown to be safe to an absolute certainty. As the House of Representatives Report on the Food Additives Amendment stated:

> Safety requires proof of a reasonable certainty that no harm will result from the proposed use of the additive. It does not — and cannot — require proof beyond any possible doubt that no harm will result under any conceivable circumstance.

H.R. Report No. 2284, 85th Cong., 2d Sess., 1958.

Aspartame has been exhaustively tested for safety and the data have been reviewed by the agency over the course of 11 years. In addition, FDA referred portions of the safety data on aspartame to outside groups of scientists for addi-

tional review, prior to approving aspartame for dry uses. The safety testing conducted for aspartame surpasses the testing requirements for direct food additives developed by the agency and set forth in its "REDBOOK" (Ref. 4). As discussed in Section I. above, the safety issues associated with the dry uses of aspartame were the subject of additional scrutiny at a hearing before the Public Board of Inquiry conducted by three scientists. Finally, the Commissioner reviewed the safety issues and the Board's conclusions on them so that he could reach a final decision on the safety of aspartame for dry uses.

After reviewing all the points raised in the objections, FDA concludes that the following issues were fully dealt with in the earlier proceeding leading to the approval of aspartame for dry uses: brain lesions and mental retardation, consumption levels, aspartame's potential for causing brain tumors, uterine polyps in rats, two human cancers and other alleged adverse reactions in clinical studies, and the quality of Searle's safety data submitted in support of the dry uses of aspartame. In the current proceeding, Mr. Turner submitted an objection covering each of these points even though, as has been pointed out before, he was a participant in the earlier proceeding. He had the opportunity to present evidence before the Board of Inquiry; he had the opportunity to question participants in that hearing; and he had the opportunity to and did file exceptions to the Board's findings. He also had the opportunity to appeal the Commissioner's decision on the dry use petition to the Court of Appeals as provided by section 409(g)(1) of the act (21 U.S.C. 348(g)(1)) or to petition for administrative reconsideration under 21 CFR 10.33. He has thus had a full and fair opportunity to present his case and have it considered in the proceeding on the dry uses of aspartame. No more is required.

The objections in the current proceeding have raised some points that present issues of law and policy, not issues of fact, specifically the allegations concerning safety testing requirements for decomposition products, consumption estimates, and labeling requirements. As explained in the specific sections discussing these points, FDA will not hold a hearing where the objection raises only issues of law or policy because these kinds of issues are not proper for resolution at a hearing.

One objection argued that because formaldehyde produced tumors at the site of administration (intranasally) in rats, FDA could not properly conclude that this metabolite of aspartame was not a systemic carcinogen. The objection offered no additional data, other than the reference to the intranasal study, that could be relied upon to solve the issue at a hearing. Considered in its factual setting, this study is inadequate to justify a conclusion that formaldehyde is a systemic carcinogen. FDA will not grant a hearing if the material submitted, even if accurate, is insufficient to justify the factual determinations urged.

Finally, the objections made a number of unsubstantiated allegations, specifically that aspartame might cause potential adverse behavioral effects, that various decomposition products of aspartame may be toxic, that the consumption estimates of aspartame are inaccurate, and that aspartame may cause cancer. In each of these cases, the objections have proferred no data on which a meaningful hearing might be based. Thus, no hearing is required on those issues.

For the reasons stated in this conclusion and in the discussion above, FDA is denying the objections and requests for a hearing.

Dated: February 17, 1984.

/s/

Mark Novitch
Acting Commissioner of
Food and Drugs

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

/s/

APPENDIX – REFERENCES

The following information has been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, and may be reviewed in that office between 9 am and 4 p.m, Monday through Friday.

1. Letter from R.J. Wurtman to Sanford A. Miller, July 21, 1983

2. Wurtman, R.J., letter to the editor, *New England Journal of Medicine,* 309:429-430.

3. Letter from P.A. LaChance to Anthony Brunetti, December 2, 1982.

4. Food and Drug Administration, "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food," FEDERAL REGISTER of October 15, 1982 (47 FR 46141).

5. Kokoski, C.J., Transcript of Aspartame Public Board of Inquiry, Vol. 1, January 30, 1980, pp. 16-24.

6. Stegink, L.D., M.C. Brummel, K. McMartin, G. Martin-Amat, L.J. Filer, Jr., G. L. Baker, and R.R. Tephly, "Blood Methanol Concentrations in Normal Adult Subjects Administered Abuse Doses of Aspartame," *Journal of Toxicology and Environmental Health,* 7:281-290, 1981.

7. Food Additive Master File 134, Studies E-60, E-61, E-64, E-65, and E-67.

8. Food Additive Master File 134, Studies E-37, E-38, E-42, E-48, E-56, and E-57.

9. Food Additive Master File 134, Studies E-50, E-68, and E-71.

10. FAP 2A3661, Memoranda from Food Additives Evaluation Branch, January 18 and March 15, 1983.

11. Food Additive Master File 134, Study E-15.

12. Food Additive Master File 134, Study E-93.

13. Martin-Amat, G., K.E. McMartin, S.S. Hayreh, M.S. Hayreh, and T.R. Tephly, "Methanol Poisoning: Ocular Toxicity Produced by Formate," *Toxicology and Applied Pharmacology,* 45:201-208, 1978.

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25. Food Additive Master File 134, Studies E-29, E-37, E-38, E-48, E-56, and E-57.

26. Letter from J. Lederer to D. Azarnoff of G.D. Searle, March 28, 1983.

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Food Additive and Animal Drug Chemistry Evaluation Branch, October 19, 1982.

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29. Food Additive Master File 134, Studies E-77 and E-78.

30. Food Additive Petition 2A2885, Memorandum from the Division of Pathology, July 28, 1975.

31. Food Additive Master File 134, Studies E-28, E-76, E-33, E-34, and E-70.

32. Kerns, W.D., K.L. Pankov, D.J. Donofrio, E.J. Gralla, and J.A. Swenberg, "Carcinogenicity of Formaldehyde in Rats and Mice After Long-Term Inhalation Exposure," *Cancer Research,* 43:4382-4392, 1983.

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APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 84-1153 September Term, 1985

Community Nutrition Institute, et al.

v.

Dr. Frank E. Young, Commissioner
Food and Drug Administration

And Consolidated Case No. 84-5253

BEFORE: Mikva, Edwards and Starr, Circuit Judges

ORDER

Upon consideration of appellants' petition for rehearing, it is

ORDERED, by the Court, that the petition is denied.

Per Curiam

FOR THE COURT
GEORGE A. FISHER, CLERK

BY: /s/ Robert A. Bonner
Robert A. Bonner
Chief Deputy Clerk

United States Court of Appeals
For the District of Columbia Circuit
FILED DEC 4 1985
GEORGE A. FISHER
Clerk

APPENDIX D

FEDERAL FOOD, DRUG AND COSMETICS ACT OF 1938, AS AMENDED

FOOD ADDITIVES

Unsafe Food Additives

Sec. 409 [348]. (a) A food additive shall, with respect to any particular use or intended use of such additives, be deemed to be unsafe for the purposes of the application of clause (2)(C) of section 402(a), unless—

(1) it and its use or intended use conform to the terms of an exemption which is in effect pursuant to subsection (i) of this section; or

(2) there is in effect and it and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used.

While such a regulation relating to a food additive is in effect, a food shall not, by reason of bearing or containing such an additive in accordance with the regulation, be considered adulterated within the meaning of clause (1) of section 402(a).

Petition To Establish Safety

(b)(1) Any person may, with respect to any intended use of a food additive, file with the Secretary a petition proposing the issuance of a regulation prescribing the conditions under which such additive may be safely used.

(2) Such petition shall, in addition to any explanatory or supporting data, contain—

(A) the name and all pertinent information con-

cerning such food additive, including, where available, its chemical identity and composition;

(B) a statement of the conditions of the proposed use of such additive, including all directions, recommendations, and suggestions proposed for the use of such additive, and including specimens of its proposed labeling;

(C) all relevant data bearing on the physical or other technical effect such additive is intended to produce, and the quantity of such additive required to produce such effect;

(D a description of practicable methods for determining the quantity of such additive in or on food, and any substance formed in or on food, because of its use; and

(E) full reports of investigations made with respect to the safety for use of such additive, including full information as to the methods and controls used in conducting such investigations.

(3) Upon request of the Secretary, the petitioner shall furnish (or, if the petitioner is not the manufacturer of such additive, the petitioner shall have the manufacturer of such additive furnish, without disclosure to the petitioner), a full description of the methods used in, and the facilities and controls used for, the production of such additive.

(4) Upon request of the Secretary, the petitioner shall furnish samples of the food additive involved, or articles used as components thereof, and of the food in or on which the additive is proposed to be used.

(5) Notice of the regulation proposed by the petitioner

shall be published in general terms by the Secretary within thirty days after filing.

Action on the Petition

(c)(1) The Secretary shall—

(A) by order establish a regulation (whether or not in accord with that proposed by the petitioner) prescribing, with respect to one or more proposed uses of the food additive involved, the conditions under which such additive may be safely used (including, but not limited to, specifications as to the particular food or classes of food in or on which such additive may be used, the maximum quantity which may be used or permitted to remain in or on such food, the manner in which such additive may be added to or used in on on such food, and any directions or other labeling or packaging requirements for such additive deemed necessary by him to assure the safety of such use), and shall notify the petitioner of such order and the reasons for such action; or

(B) by order deny the petition, and shall notify the petitioner of such order and of the reasons for such action.

(2) The order required by paragraph (1)(A) or (B) of this subsection shall be issued within ninety days after the date of filing of the petition, except that the Secretary may (prior to such ninetieth day), by written notice to the petitioner, extend such ninety-day period to such time (not more than one hundred and eighty days after the date of filing of the petition) as the Secretary deems necessary to enable him to study and investigate the petition.

(3) No such regulation shall issue if a fair evaluation of the data before the Secretary—

(A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe: *Provided,* That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal, except that this proviso shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production, if the Secretary finds (i) that, under the conditions of use and feeding specificed in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (ii) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (f) and (g)) in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal; or

(B) shows that the proposed use of the additive would promote deception of the consumer in violation of this Act or would otherwise result in adulteration or in misbranding of food within the meaning of this Act.

(4) If, in the judgment of the Secretary, based upon a fair evaluation of the data before him, a tolerance limitation is required in order to assure that the proposed use of an additive will be safe, the Secretary—

(A) shall not fix such tolerance limitation at a level higher than he finds to be reasonably required to accomplish the physical or other technical effect for which such additive is intended; and

(B) shall not establish a regulation for such proposed use if he finds upon a fair evaluation of the data before him that such data do not establish that such use would accomplish the intended physical or other technical effect.

(5) In determining, for the purpose of this section, whether a proposed use of a food additive is safe, the Secretary shall consider among other relevant factors—

(A) the probable consumption of the additive and of any substance formed in or on food because of the use of the additive;

(B) the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet; and

(C) safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimention data.

Regulation Issued on Secretary's Initiative

(d) The Secretary may at any time, upon his own initiative, propose the issuance of a regulation prescribing, with respect to any particular use of a food additive, the conditions under which such additive may be safely used, and the reasons therefor. After the thirtieth day following publication of such a proposal, the Secretary may by order establish a regulation based upon the proposal.

Publication and Effective Date of Orders

(e) Any order, including any regulation established by such order, under subsection (c) or (d) of this section,

shall be published and shall be effective upon publication, but the Secretary may stay such effectiveness if, after issuance of such order, a hearing is sought with respect to such order pursuant to subsection (f).

Objections and Public Hearing

(f)(1) Within thirty days after publication of an order made pursuant to subsection (c) or (d) of this section, any person adversely affected by such an order may file objections thereto with the Secretary, specifying with particularity the provisions of the order deemed objectionable, stating reasonable grounds therefor, and requesting a public hearing upon such objections. The Secretary shall, after due notice, as promptly as possible hold such public hearing for the purpose of receiving evidence relevant and material to the issues raised by such objections. As soon as practicable after completion of the hearing, the Secretary shall by order act upon such objections and make such order public.

(2) Such order shall be based upon a fair evaluation of the entire record at such hearing, and shall include a statement setting forth in detail the findings and conclusions upon which the order is based.

(3) The Secretary shall specify in the order the date on which it shall take effect, except that it shall not be made to take effect prior to the ninetieth day after its publication, unless the Secretary finds that emergency conditions exist necessitating an earlier effective date, in which event the Secretary shall specify in the order his findings as to such conditions.

Judicial Review

(g)(1) In a case of actual controversy as to the validity of any order issued under subsection (f), including any order thereunder with respect to amendment or repeal of a regulation issued under this section, any person who will be adversely affected by such order may obtain judicial review by filing in the United States Court of Appeals for the circuit wherein such person resides or has his principal place of business or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a petition praying that the order be set aside in whole or in part.

(2) A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall file in the court the record of the proceedings on which he based his order, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition the court shall have jurisdiction, which upon the filing of the record with it shall be exclusive, to affirm or set aside the order complained of in whole or in part. Until the filing of the record the Secretary may modify or set aside his order. The findings of the Secretary with respect to questions of fact shall be sustained if based upon a fair evaluation of the entire record at such hearing. The court shall advance on the docket and expedite the disposition of all causes filed therein pursuant to this section.

(3) The court, on such judicial review, shall not sustain the order of the Secretary if he failed to comply with any requirement imposed on him by subsection (f)(2) of this section.

(4) If application is made to the court for leave to adduce additional evidence, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper, if such evidence is material and there were reasonable grounds for failure to adduce such evidence in the proceedings below. The Secretary may modify his findings as to the facts and order by reason of the additional evidence so taken, and shall file with the court such modified findings and order.

(5) The judgment of the court affirming or setting aside, in whole or in part, any order under this section shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this section shall not, unless specifically ordered by the court to the contrary, operate as a stay of an order.

Amendment or Repeal of Regulations

(h) The Secretary shall by regulation prescribe the procedure by which regulations under the foregoing provisions of this section may be amended or repealed, and such procedure shall conform to the procedure provided in this section for the promulgation of such regulations.

Exemptions for Repeal of Regulations

(i) Without regard to subsections (b) to (h), inclusive, of this section, the Secretary shall by regulation provide for exempting from the requirements of this section any food additive, and any food bearing or containing such

additive, intended solely for investigational use by qualified experts when in his opinion such exemption is consistent with the public health.

* * * *

APPENDIX E

21 C.F.R. 1.1

§ 12.24 Ruling on objections and requests for hearing.

(a) As soon as possible the Commissioner will review all objections and requests for hearing filed under § 12.22 and determine –

(1) Whether the regulation should be modified or revoked under § 12.22 and determine –

(1) Whether a hearing has been justified; and

(3) Whether, if requested, a hearing before a Public Board of Inquiry under Part 13 or before a public advisory committee under Part 14 or before the Commissioner under Part 15 has been justified.

(b) A request for a hearing will be granted if the material submitted shows the following:

(1) There is a genuine and substantial issue of fact for resolution at a hearing. A hearing will not be granted on issues of policy or law.

(2) The factual issue can be resolved by available and specifically identified reliable evidence. A hearing will not be granted on the basis of mere allegations or denials or general descriptions of positions and contentions.

(3) The data and information submitted, if established at a hearing, would be adequate to justify resolution of the factual issue in the way sought by the person. A hearing will be denied if the Commissioner concludes that the data and information submitted are insufficient to justify the factual determination urged, even if accurate.

(4) Resolution of the factual issue in the way sought by the person is adequate to justify the action requested. A hearing will not be granted on factual issues that are not

determinative with respect to the action requested, e.g., if the Commissioner concludes that the action would be the same even if the factual issue were resolved in the way sought, or if a request is made that a final regulation include a provision not reasonably encompassed by the proposal. A hearing will be granted upon proper objection and request when a food standard or other regulation is shown to have the effect of excluding or otherwise affecting a product or ingredient.

(5) The action requested is not inconsistent with any provision in the act or any regulation in this chapter particularizing statutory standards. The proper procedure in those circumstances is for the person requesting the hearing to petition for an amendment or waiver of the regulation involved.

(6) The requirements in other applicable regulations, e.g., §§ 10.20, 12.21, 12.22, 314.200, 430.20(b), 514.200, and 601.7(a), and in the notice promulgating the final regulation or the notice of opportunity for hearing are met.

(c) In making the determination in paragraph (a) of this section, the Commissioner may use any of the optional procedures specified in § 10.30(h) or in other applicable regulations, e.g., §§ 314.200, 430.20(b), 514.200, and 601.7(a).

(d) If it is uncertain whether a hearing has been justified under the principles in paragraph (b) of this section, and the Commissioner concludes that summary decision against the person requesting a hearing should be considered, the Commissioner may serve upon the person by registered mail a proposed order denying a hearing. The person has 30 days after receipt of the proposed order to demonstrate that the submission justifies a hearing.

APPENDIX F

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 84-1153 September Term, 1984

Community Nutrition Institute, et al.,
Petitioners

v.

Dr. Mark Novitch, Acting Commissioner, Food and Drug Administration,
Respondent

United States Court of Appeals for the District of Columbia Circuit
FILED SEP 24 85
GEORGE A FISHER
Clerk

G.D. Searle & Co.,
Intervenor

PETITION FOR REVIEW OF AN ORDER OF THE FOOD AND DRUG ADMINISTRATION

Before: MIKVA, EDWARDS and STARR, Circuit Judges.

JUDGMENT

This cause came on to be heard on the petition for review of an order of the Food and Drug Administration, and was argued by counsel. On consideration thereof, it is

ORDERED and ADJUDGED, by this Court, that the order of the Food and Drug Administration under review herein is hereby affirmed, in accordance with the Opinion for the Court filed herein this date.

Per Curiam
For The Court
/s/
George A. Fisher
Clerk

Date: September 24, 1985

Opinion for the Court filed by Circuit Judge Mikva.